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Blood Lipids and Human Atherosclerosis

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The transport of cholesterol and other lipids of serum is almost wholly in the form of very large molecular complexes of these lipids with variable amounts of protein. The exact components present in the blood of a particular individual may be quantitatively described both as to character and concentration by ultracentrifugal flotation of these components in the analytic ultracentrifuge. With this technic it is possible to demonstrate the presence of certain lipid and lipoprotein components which are related to coronary atherosclerosis, to hypertension and to other diseases associated with atherosclerosis, such as diabetes mellitus, the nephrotic syndrome and hypothyroidism. The blood level of these components may be influenced by dietary means. The blood level of these components is poorly correlated with the analytic serum cholestrol determined by the Schoenheimer-Sperry method.

FOR MANY YEARS it has been suspected that the blood lipids might in some way be related to the pathogenesis of human atherosclerosis. All the major blood lipid constituents, including cholesterol and its esters, phospholipids and neutral fats, have been investigated without leading to definitive conclusions. Cholesteremia itself has received much attention, especially in view of the well-known clinical fact that certain diseases and syndromes often associated with frank hypercholesteremia (including diabetes mellitus, the nephrotic syndrome, myxedema, and familial hypercholesteremia) predispose to premature and marked atherosclerosis. However, in spite of evidence that cholesterol levels are often above 260 mg. % in persons manifesting atherosclerosis, especially in younger age groups (Morrison),[1] there is also good evidence that a high proportion of individuals develop atherosclerosis with blood cholesterols in the presently accepted normal range (125–260 mg.% by Schoenheimer-Sperry method).[2] Further, even with cholesterols above 200 mg.%, Ungerleider and his associates[3] reported that the extent of atherosclerosis in humans was not well correlated with the actual cholesterol levels.

Development of atherosclerosis in a large number of cases of normocholesteremic individuals and the low relationship manifested between the extent of atherosclerosis and serum cholesterol level has thus cast some doubt in the minds of many investigators upon the significance of serum cholesterol level, per se, in the pathogenesis of this disease. Several years ago Hirsch and Weinhouse,[4] Hueper,[5] and others speculated that possibly the phys-

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The Ultracentrifugal Group includes Mr. John Hewitt, supervising the entire group; Mr. Virgil Finster, in charge of preparative ultracentrifugation, with Russell Bjorklund, Alex Nichols, Mary Perks; Mr. Virgil Herring in charge of photography and instrumentation; and the analytic ultracentrifugal group, including Martha Kirk, Genevieve Beach, Fred Aladjem, Tod Morcott, and several technicians and graduate students who have helped on a part-time basis.

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icochemical nature of the blood lipids might be of more significance than the analytic lipid levels themselves. The majority of clinical approaches to the study of cholesteremia have involved the chemical destruction of some or all of native lipid-bearing giant molecules of serum and the subsequent lumping of the fragments into two categories, "free" and "esterified" cholesterol. Essentially none of the cholesterol in serum circulates as individual molecules of either free or esterified cholesterol, but instead is present in the form of very large molecules containing cholesterol and other lipids in association with variable amounts of protein. Several workers[6, 7] have pointed out the existence of lipoprotein molecules bearing cholesterol in human serum.

However, until recently technical difficulties precluded characterization of the individual component fractions of the lipid and lipoprotein groups in serum. Since it appeared entirely possible that there might exist in serum certain giant lipid-bearing molecules related to the development of atherosclerosis, it was evident that a method was required which would allow the identification and quantitative characterization of the individual molecular species present in the blood of an individual patient. It has been found by certain of the present authors[8] that the ultracentrifuge, under special conditions, provides a suitable tool for this purpose. With this technic, we have found and reported[9] the presence of several lipid and lipoprotein constituents in the serum of humans and rabbits and that certain types of these molecules are present when there is atherosclerosis in the human and the cholesterol-fed rabbit.

The clinical studies of atherosclerosis are necessarily described in terms of observations made with the analytic ultracentrifuge. Therefore the essential nature of the ultracentrifugal technic is given below preliminary to a description of the clinical findings themselves. This ultracentrifugal method is now crystallized into a routine test for determining the concentration of "defective" serum lipoproteins

Basic Features of the Ultracentrifuge and Ultracentrifugal Analysis

An ultracentrifuge is a device which was designed[10] for the purpose of producing forces of many thousands to many millions of times the force of gravity. Under the influence of such intense gravitational fields of force individual molecules of the size of proteins can be made to undergo sedimentation (if they are more dense than the solution in which they are present) or to undergo flotation (if they are less dense than the solution in which they are present). In either event, if the centrifugal force is sufficiently great to impart an appreciable migration rate to the molecules, a boundary becomes established between the solution containing the large molecules and the region of solution out of which these molecules have migrated. A variety of optical technics known as refractive-index gradient methods have been devised for rendering this boundary observable and for measuring the rate of movement of the boundary region itself as the centrifuge rotor spins. This technic allows calculation of a sedimentation rate or flotation rate of the molecules in a manner analogous to the familiar clinical observation of red cell sedimentation rate under the influence of gravity.

Without going into detailed theory of such optical systems, which is fully described in the literature,[10] the diagrams obtained are readily explainable and understandable. In all the studies pertinent to the atherosclerosis problem conditions are adjusted so that the molecules involved undergo flotation against the direction of the centrifugal force. Thus the optical patterns for this situation alone need be described. If there is a single species of large molecules present (of density lower than the solution in which it is present), a single boundary between solution containing the molecular species and solution free of it becomes established while the centrifuge operates. The optical system in our ultracentrifuge (Spinco Model E) uses the so-called Thovert-Philpot-Svensson technic which gives directly a picture of the refractive index gradients in the neighborhood of the protein boundary. Figure 1 shows a diagram of the ultracentrifuge cell

with a molecular species undergoing flotation, a schematic diagram of the pattern obtained, and actual photographs taken of such flotation of a single species with the aid of this optical system. It follows that if two different molecular species, migrating at different rates, are present the diagram will reveal two separate peaks as shown in figure 2. By taking photographs at successive intervals of time after the rotor has reached full speed one can determine the rate of movement of each "peak" corresponding to a molecular species and from the area over each peak one can determine the concentration of that particular species in the solution. This area is shaded in figures 1 and 2. The rate of migration of a molecule under a given set of conditions (temperature, solution composition, and centrifugal force) is a phys-

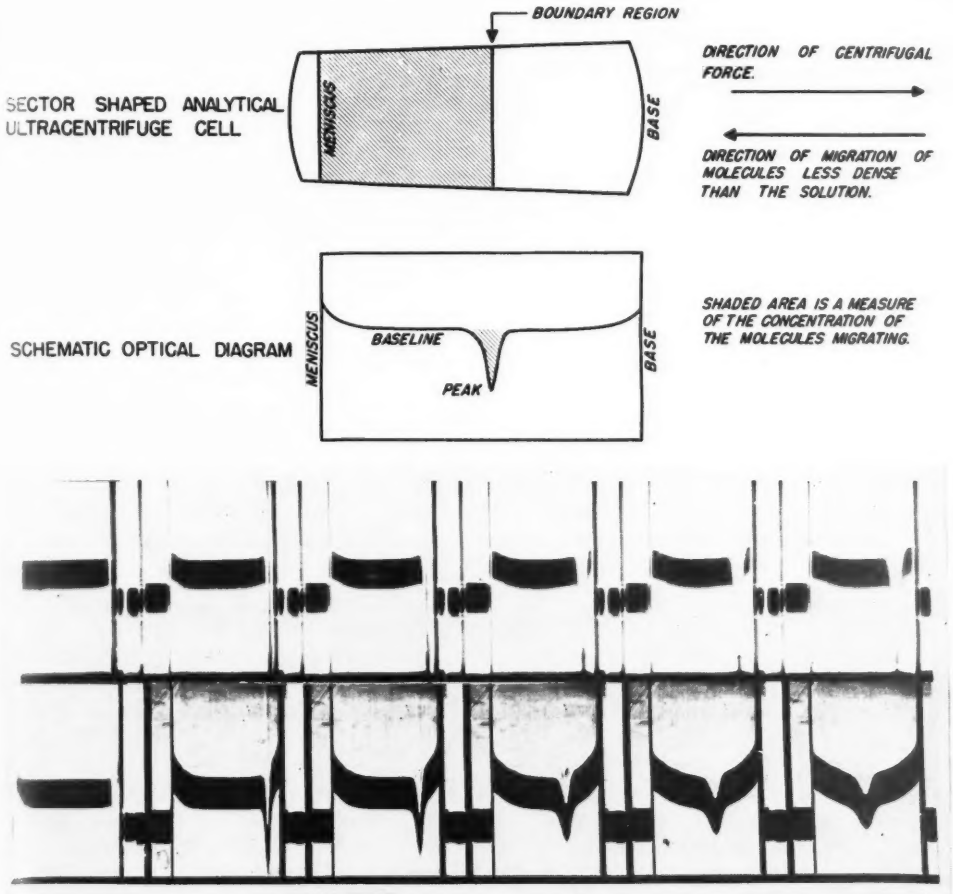

FIG. 1. Schematic diagram of ultracentrifuge cell showing migration of molecules less dense than the solution against the centrifugal force. The schematic optical diagram demonstrates the type of optical pattern obtained. Below the schematic optical diagrams are successive pictures taken from two ultracentrifuge runs, the first showing migration of isolated molecular species S_f 5.7 (rotor speed 44,770 rpm) and the second showing migration of isolated molecular species S_f 12.4 (rotor speed 52,640 rpm).

ical constant that characterizes this particular molecule in many respects better than any name we might ascribe to it.

In the work with atherosclerosis our concern is primarily with lipid and lipoprotein molecules of densities close to 1.00 Gm./cc. By adjusting the density of the solution being studied with sodium chloride to a value of 1.063, the solution is thereby made more dense than the molecules themselves, with the result that all molecules of lesser density undergo flotation. In fact in this work we preliminarily float all the lipids and lipoproteins of a class less dense than 1.063 to the surface in a preparative ultracentrifuge, pipet off the top fraction containing them, and then study the group for its individual constituents by the analytic ultracentrifugal method which gives rise to the diagrams described above. The customary unit of migration rate is the Svedberg,* named in honor of The Svedberg who invented the ultracentrifuge and developed the theory of its use. A molecule which undergoes sedimentation at a rate of 5×10^{-13} cm. per sec. per unit field of force is said to have an S value of 5, or to be a molecule of the S 5 class. We have adapted this term for flotation runs such that a molecule which undergoes flotation at a rate of 5×10^{-13} cm. per sec. per unit field of force has an S_f value of 5, or is a molecule of the S_f 5 class.

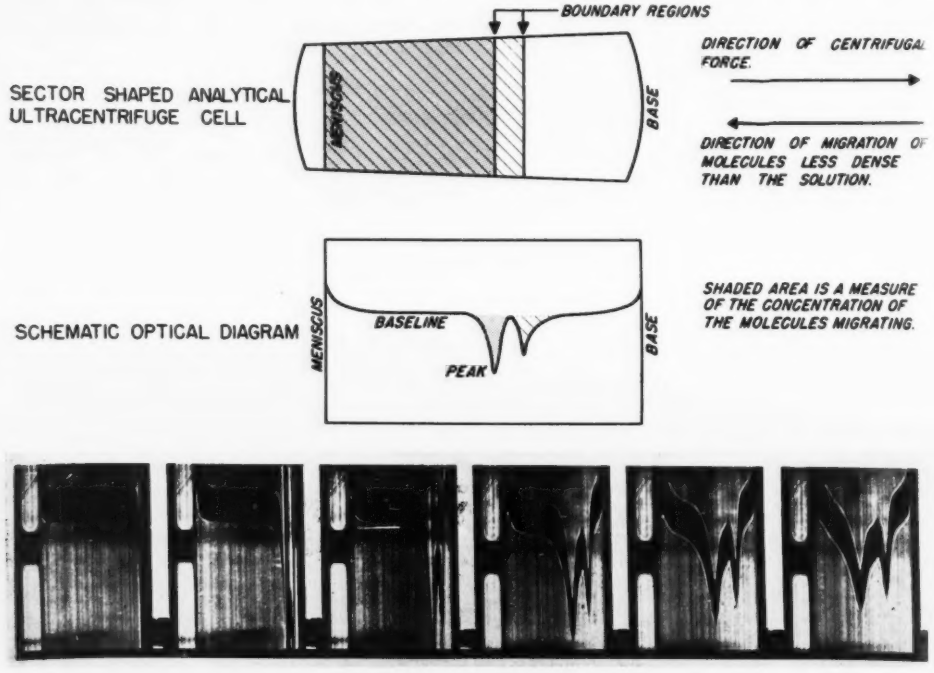

FIG. 2. Gives schematic diagrams and actual photographs where there are two major species floating with different migration rates, the larger S_f 12.4 and the smaller S_f 6.2 (rotor speed 52,640 rpm).

The Ultracentrifugal Composition of Human Serum Lipids and Lipoproteins

The group of lipoproteins and lipids in human serum of densities less than 1.063 Gm./cc.

* One Svedberg unit equals 1×10^{-13} cm./sec./-dyne/Gm. In using this unit one should specify the exact conditions under which the run was made, since the S rate will vary if the conditions are altered.

may consist of as many as ten species of molecule the number being variable from individual to individual. Several of these molecules are cholesterol-bearing molecules, and in fact generally carry a large fraction of the total serum cholesterol. These components are readily characterized by their flotation rates under specified conditions* or by their hydrated densities. For present purposes the flotation rates are most useful.

The various classes of molecules found in serum by these studies are the following:

(a) Species which migrate with S_f values greater than 75 S_f units. These include the well-known chylomicrons and aggregates of much smaller dimensions than the chylomicrons. The concentration of species in this entire class is increased following fat-containing meals and hence represents part of the alimentary lipemia. We have found no correlations between components of S_f greater than 75 units and the presence of atherosclerosis in humans.

(b) Species which migrate with S_f values between 30–70 S_f units. These species constitute the major fraction of alimentary lipemia and are greatly modified in concentration with relationship to meals. Certain of these components are cholesterol-bearing molecules and their relationship to atherosclerosis is under investigation.

(c) Species of discrete classes which migrate with rates between 10 and 20 S_f units. These components, whose molecular weights are in the neighborhood of 3,000,000, appear definitely related to the presence of atherosclerosis in humans. There are occasionally present in addition molecules of the S_f 20–30 class, some of which appear to have significance like that which characterizes the molecules of the S_f 10–20 class, but the role of the S_f 20–30 components requires further clarification. The S_f 10–20 class contains at least three separate species of molecules, each approximately 30% cholesterol by weight, which at present appear to be of equivalent significance with respect to atherosclerosis.

(d) Species which migrate with S_f rates between 3–8 S_f units. These molecules are important cholesterol, phospholipid, and protein-containing substances, loosely referred to in the general literature as the B_1-lipoprotein. Actually this component may exist as a single component or as a multiple group of components in an individual case. This component or set of components, carrying a major fraction of the serum cholesterol, is present in every one of some 4000 samples studied, at concentrations varying from individual to individual, but at an essentially constant level for a given individual from time to time. This set of components does not of itself appear to be related to atherosclerosis.

Relationship of the S_f 3–8 and S_f 10–20 Classes of Lipids and Lipoproteins to Atherosclerosis

In the serum of rabbits a set of molecules of the S_f 5–8 and S_f 10–30 class have been discovered and described[9]; these appear to be analogous to the S_f 3–8 and S_f 10–20 classes in the human. The S_f 5–8 class of molecules in the rabbit is a lipoprotein (30% cholesterol by weight) and is present in variable concentration in the serum of all normal rabbits. During cholesterol feeding of the rabbits these molecules increase in concentration first, and then level off at approximately the highest concentration achieved. Following the rise in concentration of the S_f 5–8 class of molecules, most rabbits begin to develop increasing concentrations of molecules of the S_f 10–30 class as the serum cholesterol rises as a result of further cholesterol feeding. Some rabbits, however, never go beyond the stage of development of increased S_f 5–8 concentrations, in

* The runs reported here were made at a temperature of 27 ± 2 C. in a sodium chloride solution of density 1.063 (the density being calculated independent of any contribution from proteins or lipoproteins to density), using low-density substances previously isolated by differential preparative ultracentrifugation. In the differential ultracentrifugation all the lipid and lipoprotein constituents of density less than 1.063 undergo flotation to the top of the preparative cell and are pipetted out into a volume such that these substances are concentrated by a factor of five over their initial concentration in serum. The S_f values are those obtained directly in the analytic runs without back calculation to any other set of conditions than those used in the run.

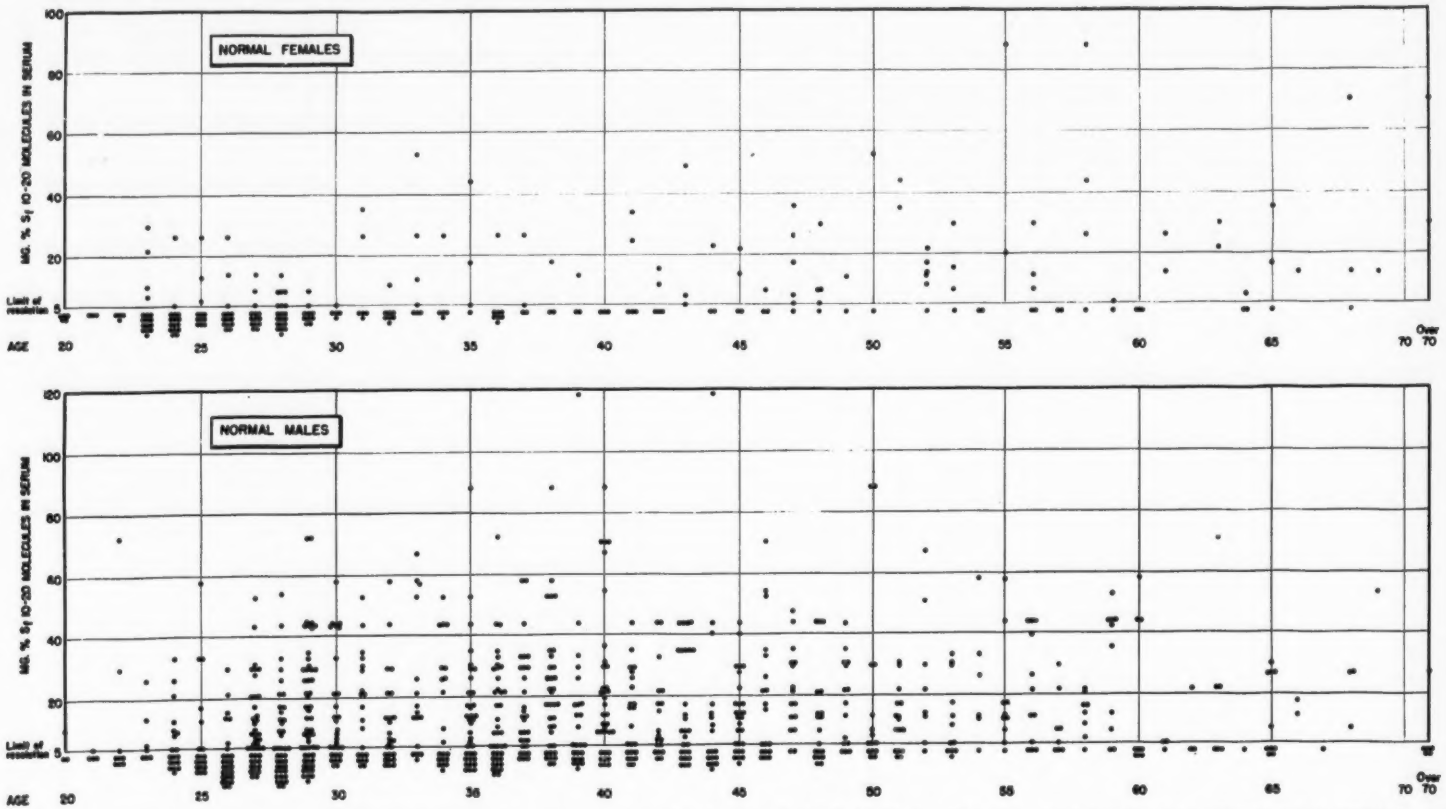

FIG. 4. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10-20 class for all normal females and normal males studied.

spite of further cholesterol feeding. Autopsy of the rabbits at the end of the 15-week feeding period has shown that the degree of atherosclerosis was greater the higher the final concentration of molecules of the S_f 10–30 class, while animals with minimal concentrations of such molecules had little or no gross atherosclerosis. Recently Simonton in this laboratory (unpublished) has studied rabbits receiving potassium iodide and cholesterol according to the procedure of Turner.[11] Three out of five of these rabbits were protected against the development of atherosclerosis and they developed at most only a very low concentration of molecules of the S_f 10–30 class, whereas the two rabbits which did develop atherosclerosis also developed appreciable concentrations of these molecules (fig. 3). By what-

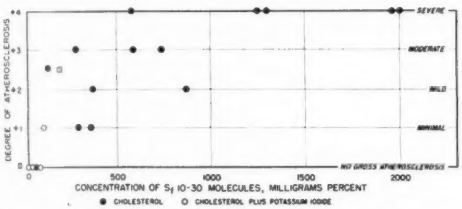

FIG. 3. Demonstration of the correlation between the severity of atherosclerosis and the terminal serum concentration of molecules of the S_f 10-30 class in the rabbit.

ever mechanism iodide protection in the rabbit operates, it certainly seemed to prevent the appearance of these molecules in the serum. In contrast with the molecules of the S_f 10–30 class, the concentration of lipoproteins in the S_f 5–8 class did not show any correlation with the extent of atherosclerosis developing either in cholesterol fed animals or cholesterol plus potassium iodide fed animals. It was of immediate interest to determine whether the group of molecules in the human (i.e., the S_f 10–20 class) analogous to the S_f 10–30 class in the cholesterol fed rabbit might bear any relationship to human atherosclerosis. The preliminary study of 280 humans, including various disease groups and many presumably normal individuals revealed that such a relation does exist. The present communication based upon a much wider experience has added confirmation to these findings and has provided several new relationships of the S_f 10–20 molecules with atherosclerosis in humans.

We have studied 1553 humans of a variety of clinical groups including patients manifesting clinical evidence of atherosclerosis, diabetes, nephrosis, hypothyroidism, hypertension, hypercholesteremia, and normals with respect to their blood content of molecules of the S_f 10–20 class, and in many cases the relationship of this to their blood cholesterol levels.

The results of all these studies are presented in the set of figures 4–9, and a summary tabulation given in figures 10, 11, 12 for ease of comparison of the various groups. The detailed discussion of the individual groups and of the significance of the findings is given below. Before commenting on the findings it is to be noted that the blood samples represent single samples from each individual. The validity of this method of sampling was checked at the outset by drawing samples of blood from 65 individuals at intervals of a few days to a few months, while they were on a steady diet and not under specific therapy, and also by drawing samples in the fasting state and again following a fat-containing meal. The results of such sampling are given in figure 13. They indicate that alimentary lipemia does not significantly affect the concentration of the molecules of the S_f 10–20 class. Further the data indicate that on a constant diet a single individual shows a reasonably stable level of concentration of such molecules, whether the concentration is low or high. As a result of these studies, it appears justifiable to use blood drawn at any time of day and to use a single sample per individual.

Living Individuals with Atherosclerosis

The best group that one can choose among living individuals who are almost certain to have atherosclerosis is a group of patients who have survived a myocardial infarction, since it is generally agreed that more than 95 per cent of myocardial infarctions occur superimposed upon coronary artery atherosclerosis. Further the diagnostic criteria for myocardial infarction are more clear-cut than for athero-

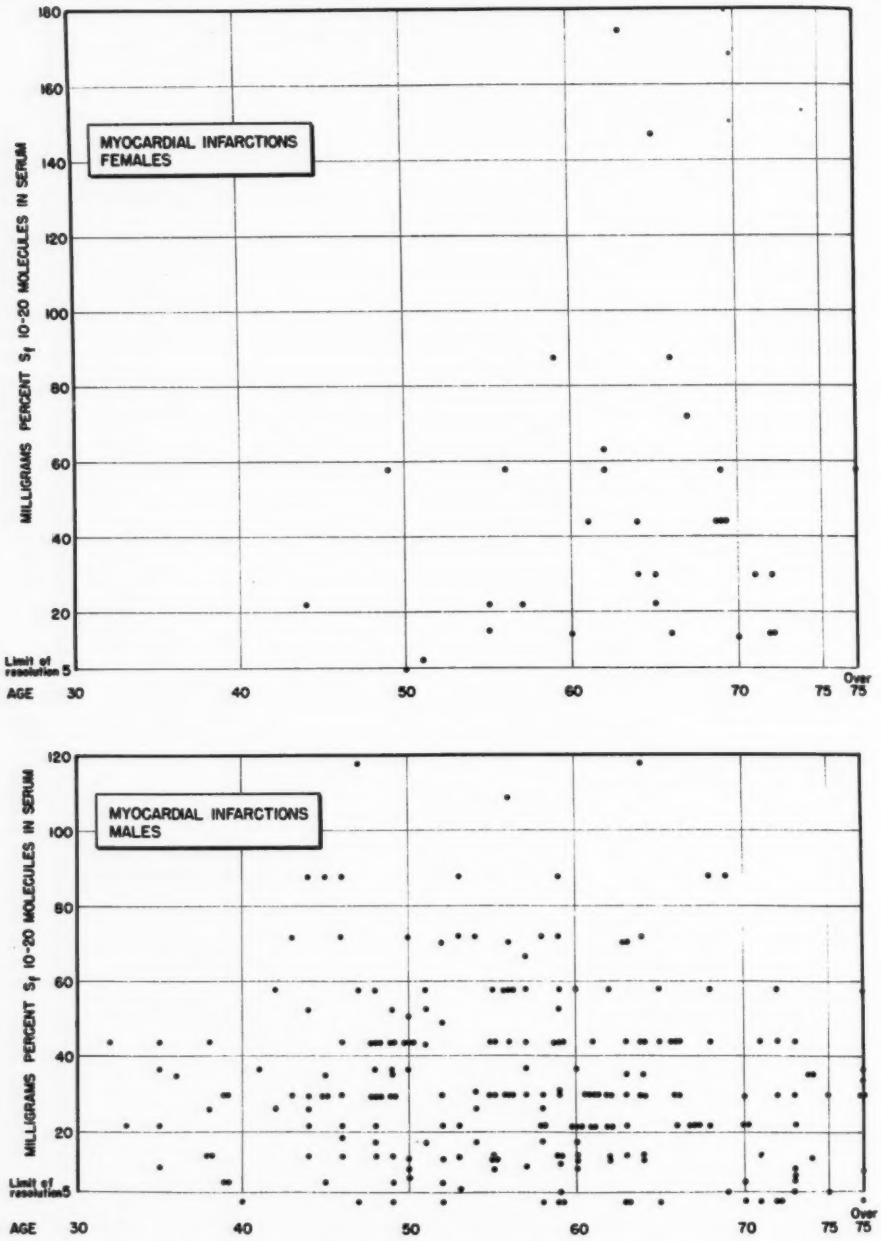

FIG. 5. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10–20 class for all female and male myocardial infarctions studied.

sclerotic complications in vascular beds other than that of the heart. The requisite criteria for inclusion in this group were (1) a typical clinical history of a myocardial infarction, (2) supportive laboratory evidence such as elevation of the sedimentation rate, leukocyto-

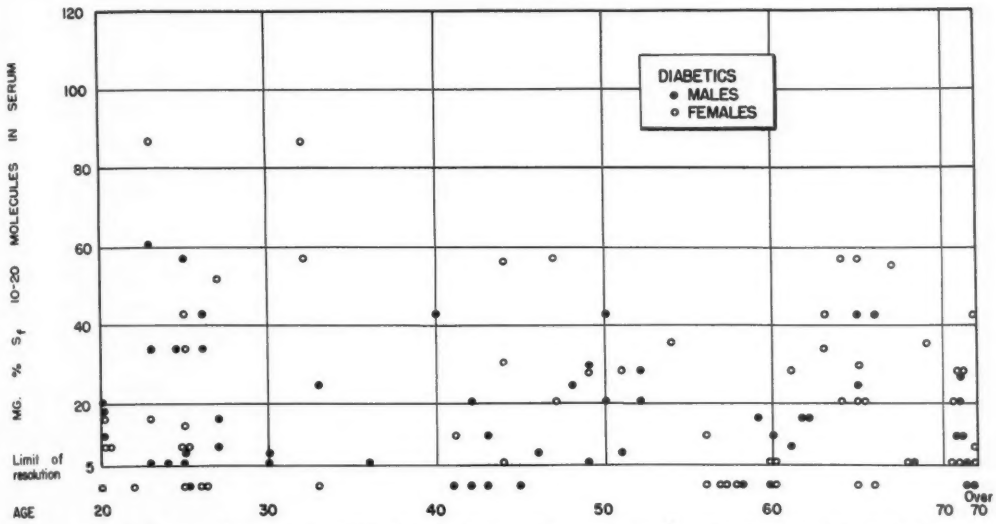

FIG. 6. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10–20 class for all diabetics studied.

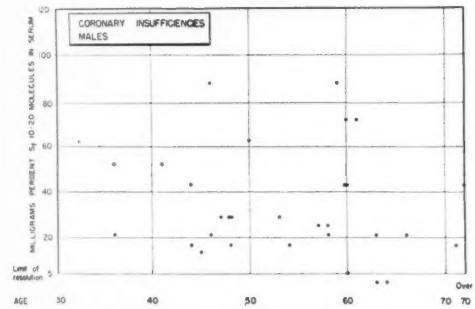

FIG. 7. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10–20 class for all coronary insufficiencies studied.

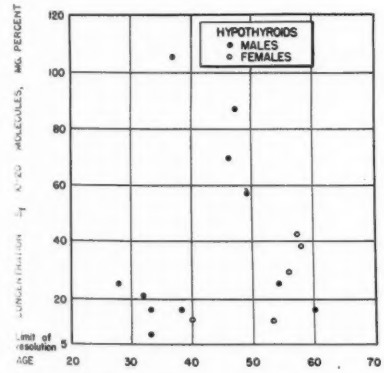

FIG. 8. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10–20 class for all hypothyroids studied.

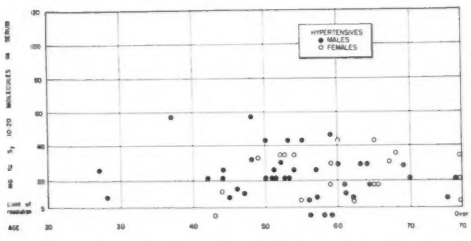

FIG. 9. Scatter diagram presenting detailed data on the concentration of molecules of the S_f 10–20 class for all hypertensives studied.

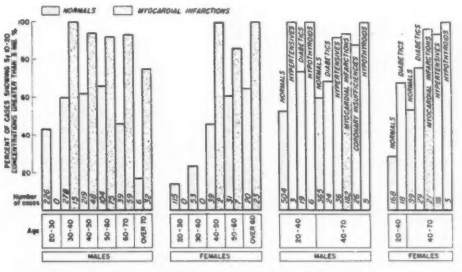

FIG. 10. Histogram summarizing the data on the incidence of concentration of S_f 10–20 molecules above the borderline level of 5 mg. % in all the disease categories studies. (Four nephrotics not plotted all showed very high concentrations of S_f 10–20 molecules).

sis, or fever, and (3) electrocardiographic changes characteristic of myocardial infarction. All cases were required to meet all three criteria. Further all cases were at least six weeks beyond the acute clinical episode, since it was desired to exclude possible metabolic disturbances of the acute phase as well as any disturbances due to dietary restrictions and drug therapy. All the patients were either on ad libitum diets or were moderately restricted relative to their diets before their infarction. For reasons explained later in this paper a small group of patients who had been on severe cholesterol and fat restriction for periods of three months to three years before their blood was studied are treated separately (independent of the measured concentrations of S_f 10–20 molecules in their blood), since they were on a regimen that we have shown (see section "Factors Affecting the Concentration of S_f 10–20 Molecules") is capable of lowering the concentration of molecules of the S_f 10–20 class in the blood. Figure 5 presents the data on 230 male patients with myocardial infarction and the data on 32 female patients with myocardial infarction. It is noted that of all the 230 males with myocardial infarction, 91 per cent of them show the presence of S_f 10–20 molecules at levels above the borderline resolution value, with an average level many times the level of limit of resolution. In the females with myocardial infarction 97 per cent of all cases show the presence of these molecules at appreciable levels. These data indicate a very high frequency of occurrence of S_f 10–20 molecules in the serum of individuals with myocardial infarction. In fact it is known that most of these patients who had been on dietary restriction of some degree were in the negative or low positive distribution of this group. However to treat the data as harshly as possible they were included in this series. We may infer, but cannot prove, that the in-

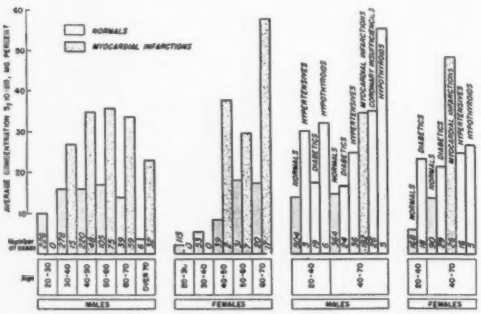

FIG. 11. Histogram giving comparison of average concentration of S_f 10–20 molecules in mg. % including all cases in all categories studied.

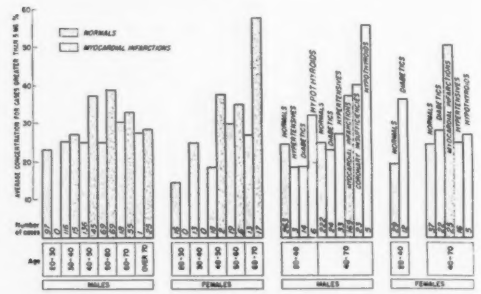

FIG. 12. Histogram giving the comparison of average concentration of S_f 10–20 molecules above the borderline level of 5 mg. % in all categories studied.

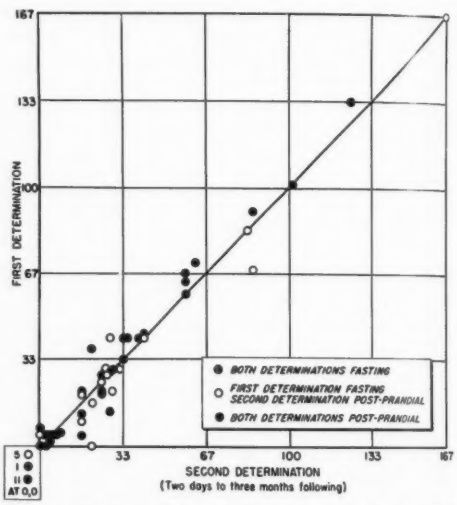

FIG. 13. A reliability diagram in which the first measurement is plotted against a second measurement two days to three months following the first. In some of the measurements the first sample was taken after a period of 12 hours fasting. If there are no individual fluctuations in the level of S_f 10–20 molecules and if there are no technical difficulties in estimating the concentration of the molecules then the points should fall exactly on the 45 degree line.

cidence of occurrence of appreciable levels of S_f 10–20 molecules might have been even higher, as might the average concentration of such molecules if this element of dietary restriction had not been present. The occurrence of the high proportion of 7 negative cases among 32 individuals over 70 years of age is interesting. Here again no proof can be given for the result obtained, although in general these people were eating considerably less than they had in earlier years. For any of the negatives there is also the possibility that some of these may fit into the small group of myocardial infarctions resulting from causes other than atherosclerosis of the coronary arteries. In any event, taking the negative results at their worst, with no effort to explain the small number of negatives in any fashion, the data of figure 11 demonstrate clearly the sharp difference with respect to incidence of appreciable concentrations of S_f 10–20 molecules in the serum of myocardial infarction patients as compared with normals of the corresponding age and sex categories. This difference is unequivocal evidence that the presence of these molecules in the serum is in some way associated with the presence of atherosclerosis. Further evidence of this association is obtained by a comparison of the average *concentration* of such molecules in serum of myocardial infarction patients with the average concentration in normals of corresponding age groups. Even if the negatives among the normals are excluded in taking the averages, the myocardial infarction groups still have a significantly higher concentration of the S_f 10–20 molecules in their serum than do the normals. That as high a percentage of presumed normals show such molecules in their blood is fully to be expected since a large proportion of such normals are certainly developing atherosclerosis although it has not yet become clinically manifest. It remains of course to be proved, however, whether or not those normals showing appreciable concentrations of these molecules in their blood represent the ones developing atherosclerosis, and whether the degree of atherosclerosis parallels the concentration of these molecules in the blood, as it appears to, in the case of the analogous molecules in the rabbit. In figures 14–17 is given the relationship between the analytic serum cholesterol levels and the concentration of S_f 10–20 molecules. It is readily seen that in the myocardial infarction group these levels do not

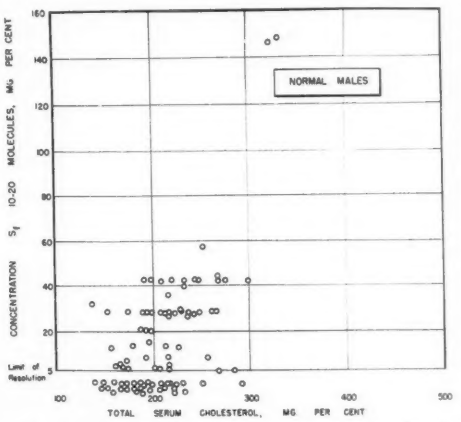

FIG. 14. Scatter diagram for normal males showing the relationship between the concentration of S_f 10–20 molecules and the concentration of total serum cholesterol (as determined by the Schoenheimer-Sperry method).

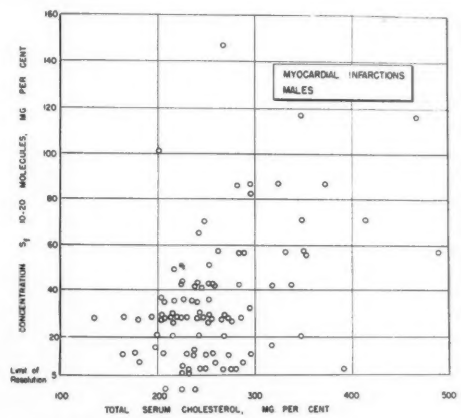
MYOCARDIAL INFARCTIONS MALES
CONCENTRATION Sf 10-20 MOLECULES, MG PER CENT
Limit of Resolution
TOTAL SERUM CHOLESTEROL, MG PER CENT

FIG. 15. Scatter diagram for male myocardial infarctions showing the relationship between the concentration of S_f 10–20 molecules and the concentration of total serum cholesterol.

correlate well. For example at 200 mg.% total cholesterol a patient may have a manyfold greater concentration of S_f 10–20 molecules than will another patient at 300 mg.%. If our hypothesis of the relationship of these

molecules to atherosclerosis is correct, this finding might explain the low relationship indicated in previous studies between degree of atherosclerosis and the serum cholesterol levels.

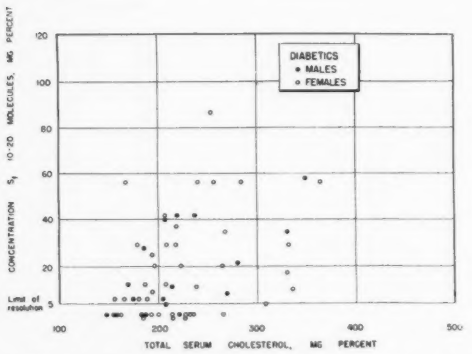

FIG. 16. Scatter diagram for diabetics showing the relationship between the concentration of S_f 10–20 molecules and the concentration of total serum holestero

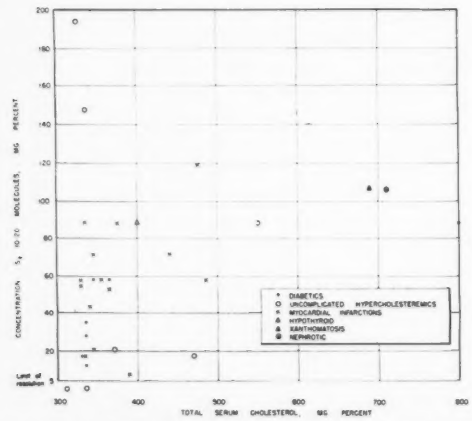

FIG. 17. Scattesr diagram for hypercholesteremics of various originn showing the relationship between the concentratiot of S_f 10–20 molecules and the concentration of toal serum cholesterol.

Individuals Showing No Demonstrable Vascular Disease:

A large series of men and women without known disease in representative adult age categories has been studied for the concentration of molecules of the S_f 10–20 class in the blood. Over 90 per cent of this group had had a recent physical examination, the record of which was available to us. Thus it was possible to exclude from this "normal" category any patients with sustained hypertension or diabetes (at least diabetes resulting in glycosuria). Individuals with rheumatic fever histories, nephritis histories, rheumatoid arthritis, or any known malignancies were also excluded. It must be emphasized that many of these individuals are undoubtedly developing atherosclerosis even though there is no clinical manifestation. There is no known method for the objective selection of living individuals with respect to presence or absence of atherosclerosis unless there has been a clinical manifestation of vascular disease. Since among this group there will still be a large proportion of persons free of atherosclerosis or with minimal atherosclerosis, it would be expected that this group should show a relatively lower average rating than groups with known atherosclerotic disease on any scale indicative of this disease. In all age categories and in both sexes, patients with proved myocardial infarction show a consistently greater incidence and average concentration of molecules of the S_f 10–20 class than do the above-described normal controls. This supports our hypothesis of the association of the molecules of the S_f 10–20 class with atherosclerosis. Further the incidence and concentration of such molecules in the blood of our presumably normal individuals are in agreement with the data reported in the literature[12] on the incidence and degree of atherosclerosis found in autopsy material as a function of age. Of particular interest is the increase in incidence and concentration (see figure 10) in males with aging at least up to the 50–60 year age categories. Whether the apparent decrease after 60 years is significant must await more extensive data on the older age group. The very low incidence and average concentration of S_f 10–20 molecules in the serum of young women is in good accord with the relative rarity of atherosclerosis and its complications in young women. The marked change in the women especially above 40 years of age coincides with the fact that women lose their apparent relative protection against the complications of atherosclerosis with increasing age.[13] An endocrine factor suggests

itself but will require study for identification and evaluation.

Individuals with Diabetes Mellitus:

The increased occurrence of atherosclerotic complications in diabetics as compared with the general population of the same age group is well known. It was therefore of interest to determine the blood picture in such subjects with respect to the presence of molecules of the S_f 10–20 class. For this 76 patients with diabetes mellitus of age 20–80 years have been studied. These represent diabetics varying widely in the quality of control and insulin requirements. No effort is made here to correlate these factors with the blood findings since a much larger group in each age and sex category will be required for this purpose. However, considering the group as a whole certain definite conclusions can be drawn from the data, which are presented in figures 6 and 11. The female diabetics demonstrate a distinctly higher incidence of appreciable concentration of molecules of the S_f 10–20 class than do normal females in all age categories. The effect is relatively great in the diabetic females between 20–40 years of age. The same general effect is observed in diabetic males as compared with normal males, but is not as large as for the females. The study of a larger number and a classification with respect to severity of the diabetic state is necessary.

Individuals with Coronary Insufficiency:

A group of 30 males who presented the clinical picture of angina pectoris and coronary insufficiency, but who had never had a proved myocardial infarction, has been studied. These patients had either normal electrocardiograms or minor ST-T wave changes. It would be anticipated that, since none of these patients were anemic, the most probable cause of their coronary insufficiency would be atherosclerotic involvement of the coronary arteries, with a high likelihood, from the work of Blumgart and Schlesinger,[14] that coronary occlusions were present. The data are presented in figure 7. It is seen that 90 per cent of the 30 cases showed the presence of appreciable levels of molecules of the S_f 10–20 class. This result is in accord with the data on patients with proved myocardial infarction, as might be expected since the basic pathology is similar for the two groups. The result is also further evidence consistent with the hypothesis that the molecules of the S_f 10–20 class are associated with atherosclerosis.

The Nephrotic Syndrome:

To date only 4 patients with the nephrotic syndrome have been studied with respect to the blood level of molecules of the S_f 10–20 class. Although the group is small, the results are sufficiently striking to deserve comment. In all 4 cases exceedingly high concentrations of molecules of the S_f 10–20 class are present in the serum. These levels are in fact among the highest we have yet observed, being 105, 149, 175, and 420 mg. %. The last value, 420 mg. % S_f 10–20 molecules, was from a 6 year old child who has since come to autopsy after two years of the nephrotic stage of her disease. The abdominal aorta showed extensive atherosclerosis.

Hypothyroidism:

Patients with marked hypothyroidism are known to be subject to excessive atherosclerosis as compared with euthyroid individuals. A group of 16 patients who presented clinical features of hypothyroidism, low basal metabolic rates and, in most cases, serum cholesterols over 300 mg. % have been studied. Two of these were frank cases of myxedema who were already receiving thyroid replacement therapy. Most of the others were receiving thyroid extract, although in some of these it was not felt that they were yet receiving the optimal dose. The data, presented in figure 8 and figure 10 show that *all* of these cases had appreciable concentrations of molecules of the S_f 10–20 class in the serum. Had these patients not already been on thyroid therapy it is likely that they might have shown an even higher average concentration of S_f 10–20 molecules. In our current studies we are endeavoring to study the blood of hypothyroid patients before and during thyroid therapy. The data presented on hypothyroid patients are consistent with the general occurrence of

the S_f 10–20 molecules in diseases predisposing to atherosclerosis.

Hypertension:

Although it has never been shown that atherosclerosis is etiologically related to hypertension, the very common occurrence of atherosclerosis and its complications in sustained hypertensive disease is well known. A group of 39 men and 16 women with sustained hypertension (diastolic pressures repeatedly observed above 100 mm. Hg) have been studied. No hypertensives who had already demonstrated clinical evidence of coronary artery disease are included in this group. Many of the cases studied were on weight reduction and salt-restricted diets at the time of the blood study. The effect of dietary restriction, from studies reported in a later section of the communication, would in general be to reduce the concentration of S_f 10–20 molecules in the serum. In spite of this it is seen (figs. 9 and 10) that 92 to 94 per cent of the hypertensives show the presence of appreciable levels of S_f 10–20 molecules in the serum, a value significantly higher than that of corresponding normals. These studies are being continued with untreated hypertensives to provide a group which can be more properly compared with the corresponding normals. The increased frequency of occurrence of appreciable levels of molecules of the S_f 10–20 class suggests the possibility that atherosclerotic complications in hypertensive patients may be in part, at least, on this basis. Any relationship of the presence of the S_f 10–20 molecules to the hypertension itself must await further evaluation.

Relationship of the S_f 10–20 Molecules to the Analytic Serum Cholesterol Levels:

In figures 14, 15, 16, and 17 are given the levels of S_f 10–20 molecules plotted against the analytic serum cholesterol levels for some of the normal males, diabetics, the group of patients having had a myocardial infarction and various hypercholesteremic patients. (All analytic cholesterol values were determined by a modification of the Schoenheimer-Sperry method). It is seen from the data for normals that the serum level of S_f 10–20 molecules may be very low or very high at a particular serum cholesterol level.

Tabulated below from figures 14 and 15 are the summarized data for normal males and males with myocardial infarction with respect to the relationship of S_f 10–20 component levels as compared with analytic serum cholesterols. Within the analytic cholesterol range below 300 mg. % and below S_f 10–20 levels of 44 mg. % is an area which comprises more than 95% of the tested normal male population and 75% of the studied myocardial infarctions. It is this group which is tabulated.

As can be seen from table 1 and from figures 14–17, there is a general trend toward higher S_f 10–20 concentrations with higher serum cholesterol levels, but for any particular patient the analytic serum cholesterol level is of no value in predicting the concentration of S_f 10–20 molecules. From figures 15, 16 and 17 it is seen for patients in many categories with hypercholesteremia (over 300 mg. %) that the chance of S_f 10–20 molecules being present at appreciable concentration is much greater, but even here the actual level of S_f 10–20 molecules is poorly related to the analytic serum cholesterol levels.

TABLE 1

Number of Cases	Range of S_f 10–20 Concentration	Range of Analytical Cholesterol Levels	Average Serum Cholesterol
	mg%	*mg%*	*mg%*
Myocardial infarctions			
41	24–44	134–295	231
27	6–24	164–295	235
Normal males			
30	24–44	136–294	224
16	6–24	155–282	198
41	Less than 5	140–292	196

Assuming our hypothesis of the relationship of molecules of the S_f 10–20 class to atherosclerosis to be correct, all these observations taken together may reveal the difficulty in trying to establish any correlation of the analytic serum cholesterol levels with the presence or severity of atherosclerosis. Since there is a trend toward higher S_f 10–20 mole-

cule levels with higher cholesterols, the observed general shift of the myocardial infarction patients toward higher analytic cholesterol levels would be anticipated on the basis of our hypothesis.

Factors Affecting the Concentration of S_f 10–20 Molecules:

Early in our studies a large group of individuals were studied both before and after a single meal containing fat and cholesterol. In no case was it possible to demonstrate any acute effect on the blood concentration of S_f 10–20 molecules from a single meal. Alimentary lipemia affects the components of the 40 S_f and greater group but not those of the S_f 10–20 group. Testing numerous individuals on two or more occasions revealed that the level of S_f 10–20 molecules was essentially stable provided that the subjects did not change their dietary habits (see fig. 13).

In the rabbit the atypical molecules of the S_f 10–30 class appear in the serum after a period of cholesterol feeding. Such molecules have never been observed in any of more than 50 normal rabbits of the same stock. In the cholesterol fed rabbit it was invariably found that the atypical molecules of the S_f 10–30 class appeared only after a preliminary rise in the concentration of the normally-occurring lipoprotein of the S_f 5–8 class. It thus appeared that the atypical molecules of the S_f 10–30 class might represent the results of an overflow above the capacity of the rabbit to handle the excess cholesterol via the normally-occurring lipoprotein of the S_f 5–8 class.

It was of interest to know whether any similar type of change in cholesterol metabolism operated in the human. Therefore, a group of men and women have been placed on a low fat, low cholesterol diet and their serum levels of S_f 10–20 molecules followed for as long as 16 weeks of dieting. Regardless of the initial concentration of the S_f 10–20 molecules most of the individuals showed consistent trends to lower concentrations of the molecules. There is marked individual variation in the rate of its reduction; some of the subjects exhibited rapid reduction reaching concentrations below the limit of resolution in 2 to 3 weeks. Others during the first few weeks showed no change or even rarely an increase. However, the great majority of subjects who have remained on the diet for longer than four weeks have shown considerable reduction in the S_f 10–20 component.

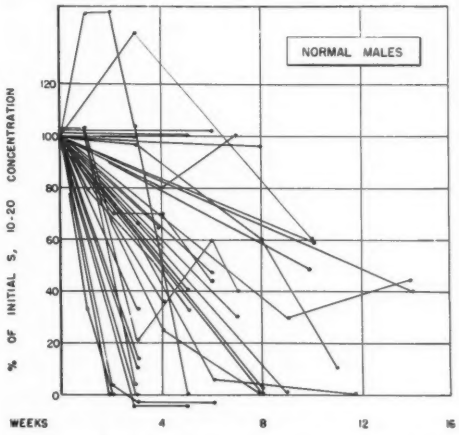

FIG. 18. Plot of the effect of a low fat, low cholesterol diet on the concentration of S_f 10–20 molecules in a series of normal males eating at home or in restaurants.

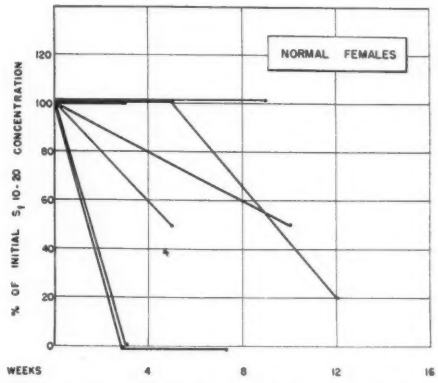

FIG. 19. Plot of the effect of a low fat, low cholesterol diet on the concentration of S_f 10–20 molecules in a series of normal females eating at home or in restaurants.

These studies are individually graphed in figures 18–21. One of these groups (fig. 21) is a study of a selected group of S_f 10–20 positive individuals who ate all food (except a breakfast which was composed of fruit, cereal, skim milk and coffee) at the diet-kitchen table of

Cowell Hospital (University of California). These meals were prepared using measured amounts of cholesterol-containing foods.[15] Between 100 and 200 Gm. of lean meats, which average about 100 mg. of cholesterol and 15

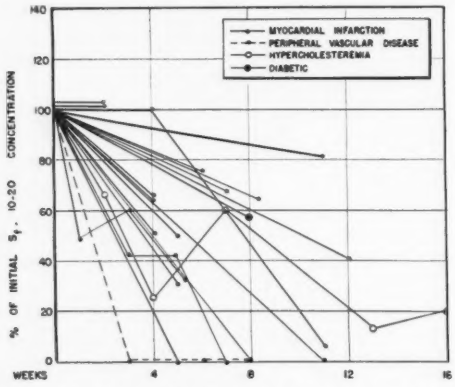

FIG. 20. Plot of the effect of a low fat, low cholesterol diet on the concentration of S_f 10–20 molecules in patients with a variety of diseases including myocardial infarction, peripheral vascular disease, hypercholesteremia, and diabetes, eating at home or in restaurants.

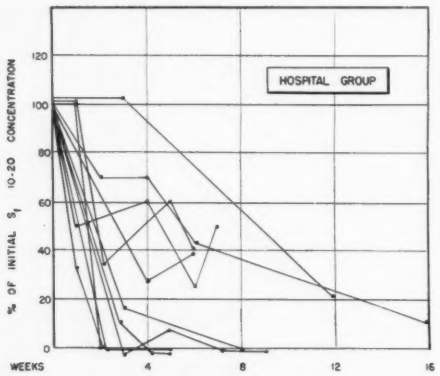

FIG. 21. Plot of the effect of a low fat, low cholesterol diet on the concentration of S_f 10–20 molecules in a small group of patients who received their luncheon and dinner at a controlled hospital diet table.

Gm. of fat per 100 Gm.,[15] were used. The total intake of cholesterol per day was kept about or below 200 mg. per person. Intake of animal fat was avoided except for that contained in the lean meats; the total of animal and vegetable fats were kept at about 50 Gm. per day. Approximately half of the subjects in every category listed in figures 18–21 restricted their caloric intake during a period of adjustment to the diet. These individuals demonstrated no differences in their response to the low cholesterol, low fat diet from those who had not appreciably diminished their caloric intake. The uniform and rapid reduction which generally occurred in the hospital-controlled dietary group as contrasted with the less uniform and slower response of those who were on the diet at home suggests that the latter group may not have followed the restrictions as closely as the former group. Several individuals were returned to their normal diets after showing a marked drop in S_f 10–20 component concentration during a period of dietary restriction. Most of these have shown a rise in concentration of these molecules in a period of four weeks. From figure 20 it is seen that the effect of dietary restriction in patients having had a myocardial infarction in the past does not differ from that in normal males. Analytic serum cholesterols determined on many of the subjects on the diet revealed that in some cases a fall in concentration of S_f 10–20 molecules was accompanied by an appreciable fall in total cholesterol whereas in many other cases it was not.

Detailed dietary histories were analyzed for 43 persons demonstrating a wide range of S_f 10–20 component concentration. There was no consistent relationship between the dietary cholesterol or fat intake and the blood level of S_f 10–20 molecules in the group as a whole. This would suggest that there is a wide range of individual tolerance to the usual levels of these substances in the diet.

It has been possible to study an additional small group (19 patients) who had had a myocardial infarction and who had been, at the advice of physicians, on a strict low fat and low cholesterol diet for periods of three months to three years before we had the opportunity to examine their bloods for the level of S_f 10–20 molecules. The data presented in figure 22, shows that this group has a lower concentration of molecules of the S_f 10–20 class than either

normals or our other myocardial infarction patients of corresponding age and sex categories. This represents indirect supportive evidence of the efficiency of dietary restriction to reduce the concentration of the S_f 10–20 molecules in the serum.

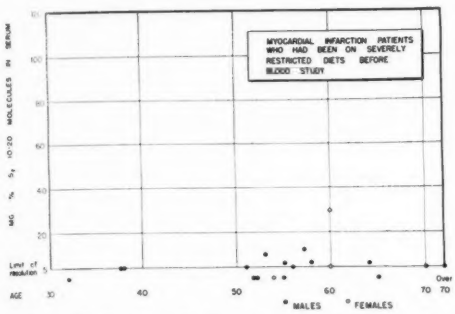

FIG. 22. Scatter diagram of a small group of patients with myocardial infarction who had been placed by their physicians on a low fat, low cholesterol diet for a period of 3 months to 3 years before their blood was studied. It is worthy of note that this group showed a lower concentration of S_f 10–20 molecules than the major group of myocardial infarctions and also lower than the normals of the corresponding age and sex categories.

SUMMARY

The presence of a class of lipid and lipoprotein molecules in the serum of man and the cholesterol fed rabbit, associated with atherosclerosis in both species, has been demonstrated.

These molecules do not represent any part of the acute alimentary lipemia. The presence of these cholesterol-bearing lipid and lipoprotein molecules cannot be predicted from the analytic total serum cholesterol level. Partial dietary restriction of fat and cholesterol in man results in a gradual decrease in the serum level of such molecules over a period of weeks to months.

These molecules are present with a much higher frequency and at higher concentrations in patients who have survived a myocardial infarction than in corresponding individuals without known vascular disease. The presence of these molecules with increased frequency in other diseases associated with excessive atherosclerosis (diabetes mellitus, the nephrotic syndrome, hypothyroidism, hypertension, and coronary insufficiency) supports the hypothesis of their association with atherosclerosis.

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Impending Hemorrhagic Shock and the Course of Events following Administration of Dibenamine

By Harold C. Wiggers, Ph.D., Harold Goldberg, M.A., Frank Roemhild, M.A., M.D., and Raymond C. Ingraham, Ph.D.

By blocking sympathogenic vasoconstrictor mechanisms with dibenamine, a dog's tolerance to severe hemorrhagic hypotension states is definitely improved. New evidence is presented that partial release from vasoconstriction achieved by giving small doses of dibenamine during the impending shock state seems to provide animals with even greater tolerance to this standardized form of stress. Although the use of dibenamine clinically for this purpose seems contraindicated, the dangers of administering vasoconstrictor drugs to patients in impending shock are emphasized.

DURING AND following the severe reduction of the circulating blood volume which results from extensive hemorrhage, sympathogenic vasoconstrictor mechanisms appear to be greatly activated.[1, 2] As a consequence, the diminished blood volume is partially compensated. The reduction in the capacity of the total vascular bed renders more efficient the accommodation of the remaining blood volume, to the extent that the blood supply to the heart and brain are the best possible under these hemorrhagic conditions. Hence, the *initial* beneficial though temporary effects of vasoconstriction, providing the interval between the cessation of hemorrhage and the restoration of blood volume to normal is not unduly prolonged, must be recognized. It is equally obvious, however, that the reasonably adequate blood supply to the heart and brain is maintained at the expense of a marked reduction in blood flow to such organs as the liver, kidney, intestines and skin where vasoconstriction becomes intense. If, therefore, either by experimental intention or clinical impracticality, the period of hemorrhagic hypotension is prolonged, the existing *impending* shock state progresses rather rapidly to one of *irreversibility*, in which repeated transfusions prove futile.[3]

It is recognized, furthermore, that hypotension, per se, reduces greatly the peripheral circulation. When superimposed vasoconstriction is not a factor, however, the period of severe hypotension (after histamine) which can be withstood without the development of irreversible shock, is many times greater than that seen in hemorrhagic hypotension.[4] Whereas there is probably no significant redistribution of flow from the less vital to the more immediately vital organs in histamine hypotension, hemorrhage and its attendant vasoconstriction lead to severe reductions in peripheral blood flow. Since vasoconstriction leads to ischemia in many regions, it is reasonable to assume that the auto-infusion of tissue fluids in the capillaries of these ischemic areas is greatly impaired, thus reducing the net compensatory fluid replacement volume.

With the thought in mind that severe, prolonged vasoconstriction hastens the rate of transition from impending to irreversible shock, studies were carried out on dogs whose sympathogenic vasoconstrictor mechanisms had been functionally blocked prior to the onset of bleeding.[5] It was observed that dogs given 15 to 20 mg. per Kg. doses of dibenamine hydrochloride some twenty hours prior to the onset of hemorrhage tolerated the standardized hemorrhagic hypotension procedures better than untreated control dogs. Not being satisfied

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with the conclusiveness of the evidence obtained, the studies were extended to the series reported in this paper. It seemed advisable, in this series, to permit a group of animals to endure the impending shock state for about 45 minutes before administering the adrenergic blocking agent. Most control animals at the end of 45 minutes of hemorrhagic hypotension have been found to be just at the point of transition from impending to irreversible shock. It was also decided to reduce the dosage of dibenamine, in an attempt to provide only partial rather than complete inhibition of the vasoconstrictor mechanisms.

Procedure

Forty healthy mongrel dogs, varying in weight from 7.7 to 23.2 kilograms, were used. All were subjected initially to the same operative and hemorrhagic procedures. Under local procaine hydrochloride anesthesia, (a) a femoral artery was cannulated for rapid hemorrhaging and for the continuous registration of mean arterial pressure with a mercury manometer, (b) the other femoral artery was exposed for repeated blood sampling, and (c) a femoral vein was cannulated for the eventual reinfusion of the blood withdrawn during the hemorrhagic period.

After adequate control measurements had been made, each dog was rapidly hemorrhaged until arterial pressures reached a level of 35 to 38 mm. of Hg. The bleeding rate varied between 50 to 75 ml. per minute and the onset of the hemorrhagic-hypotension period was attained within a bleeding period of 7 to 10 minutes. The blood withdrawn to induce this degree of hypotension was collected in a graduate cylinder, which contained adequate quantities of the anticoagulant, Liquaemin*, and was measured. This volume, referred to as the *initial bleeding volume* (IBV), averaged about 37 ml. per Kg. in control dogs, although considerable variation was noted (see table 3).

During the ensuing 90 minutes, the hypotensive level was constantly maintained by means of an automatic pressure stabilizer device (after the method of Lamson[6]). A calibrated reservoir bottle, partially filled with a known quantity of the withdrawn heparinized blood, was connected to the side arm of a femoral arterial cannula. This reservoir was then elevated to the level required to maintain the established hypotension level (35 to 38 mm. of Hg). Thus, as compensatory mechanisms were mobilized following the initial rapid hemorrhage, any consequent tendency for arterial pressure to rise above 35 to 38 mm. of Hg was abruptly arrested by automatic bleeding from the dog into this reservoir. Contrarily, in the later stages of the 90 minute hypotension period if compensatory mechanisms became exhausted, any tendency for arterial pressure to decline below the established level was prevented by immediate automatic infusion of withdrawn blood from the reservoir into the animal. Reservoir blood volumes were carefully observed and recorded at 5 to 10 minute intervals or more frequently when necessary.

The maximal quantity of blood which slowly accumulated in the reservoir during hypotension plus the IBV is referred to as the *maximal bleeding volume* (MBV). Subtracting the IBV from the MBV yields that amount of blood which was slowly and automatically withdrawn from the animal to sustain the 35 to 38 mm. of Hg blood pressure level. This is referred to as the *secondary bleeding volume* (SBV). It was quite variable in volume (see table 3) and was always considerably less than the IBV. The volume of withdrawn blood which remained to be reinfused at the termination of the 90 minute hypotension period is called the *net-total bleeding volume* (N-TBV). Though occasionally identical, especially in control dogs which survived, the N-TBV was usually less than the MBV. This discrepancy signifies the amount of blood which was automatically reinfused during the late stages of the 90 minute hypotension period. This *automatic reinfusion volume* (ARV); that is, the MBV minus the N-TBV, was of considerable diagnostic significance in the control dogs.

After 90 minutes of hypotension, the remaining blood (N-TBV) was filtered through cotton gauze and reinfused via a femoral vein. Following this replacement of all withdrawn blood, the wounds were carefully sutured and the dogs were returned to their quarters. They were observed for 72 to 96 hours or until irreversible shock intervened. Animals in good condition after 72 hours were considered to have recovered completely. Those succumbing within that interval usually did so within 12 hours and were considered as shock fatalities.

Twenty dogs served as untreated controls. The other 20 dogs were "test" animals which received dibenamine. Since complete inhibition of sympathogenic vasoconstrictor mechanisms was not desired, preliminary tests were conduced to ascertain the dose of dibenamine which would afford partial inhibition or release from vasoconstriction. As an arbitrary criterion, a dose was selected which, when injected during hemorrhagic conditions, most constantly prevented large elevations of arterial blood pressure in response to pressor doses of adrenaline (3–5 μg. per Kg. intravenously) and which would not induce the profound "adrenaline reversal" commonly obtained with doses yielding complete block-

* We are sincerely indebted to Roche-Organon, Inc. for their generosity and cooperation in supplying us with the quantities of Liquaemin required to execute this study.

ing. As might be expected, this dose varied from animal to animal. It was decided that our purpose could best be accomplished if the dibenamine was given in doses of 3 mg. per Kg. to all test dogs. It was administered in 15 to 20 ml. of 0.9 per cent saline via femoral vein just 30 minutes after the onset of the 90 minute hypotension period. This moment for the injection of dibenamine was selected (a) because it was desired to induce partial reduction of existing vasoconstriction at the midpoint of the 90 minute hypotension period and (b) because it generally requires about 15 minutes for dibenamine to approach maximal effectiveness as an adrenergic blocking agent. Unfortunately, it was impractical to employ the adrenaline test as a measure of dibenamine action during the course of the hypotensive period. It was noticed, however, that 15 minutes after dibenamine injection, previously dilated pupils constricted to less than prehemorrhage dimensions. An attempt was made to test the effectiveness of the dibenamine by comparing the blood pressure response to 3 μg. per Kg. doses of adrenaline given intravenously before and after the hypotension period. In table 1 the results are tabulated such that comparisons may be made between pre- and posthemorrhagic responses to identical doses of adrenaline among the dogs which received dibenamine. A few of the prehemorrhagic responses in the early experiments were inadvertently omitted. Pre- and posthemorrhagic responses to adrenaline among control dogs were not significantly different. In general, the authors believe that the desired partial inhibitory influences of dibenamine were obtained, if the response to adrenaline is accepted as a satisfactory criterion. There were obviously quantitative differences in the individual animals which were beyond control.

TABLE 1.—*Blood Pressure Response to Adrenaline*

Dog No.	Prehemorrhagic response to adrenaline 3 μg./Kg.	Posthemorrhagic post-dibenamine response to adrenaline 3 μg./Kg.
	mm.Hg	*mm.Hg*
1		−30
2		+20
3	+50	−5
4		+10
5		0
6		0
7	+70	−20
8	+50	0
9*		+ 10, then −20
10	+50	+15
11	+40	0
12	+100	+10
13*	+35	+20
14	+80	−25
15	+50	+10
16	+60	+20
17	+50	−10
18	+60	−20
19	+70	−10
20	+70	0

* These represent the 2 fatality dogs. See text for discussion.

RESULTS

The results show that the dibenamine, in the amounts given, did alter the course of events during the second half of the hypotension period. It altered them to the extent that in most of the dogs, the transition from impending to irreversible shock did not occur as it did in 70 per cent of the untreated control dogs. The comparative survival rates are presented in table 2. It is seen that, following reinfusion of the N-TBV at the end of the hypotension period, only 6, or 30 per cent, of the untreated control dogs recovered. The post-reinfusion survival times among the 14 who died in shock varied from 1 to 36 hours, 12 of these succumbing within a 12 hour period.

TABLE 2.—*Survival Rate following Hemorrhage*

Series	No. of Dogs	C.R.	F.	% C.R.
Controls	20	6	14	30
Dibenamine 3 mg./Kg.	20	18	2	90

C. R. = complete recovery dogs.
F. = fatality (irreversible shock).

In striking contrast, only 2 of the 20 dogs which received dibenamine entered the irreversible state and succumbed; within 4 and 36 hours after reinfusion, respectively. This indicates that the transition from impending to irreversible shock did not occur in 90 per cent of these dogs.

The question arises as to whether the dibenamine group were subjected to as intense a degree of impending shock as the untreated controls. From the comparative data on bleeding volumes presented in table 3, it would seem that one could argue for or against such a belief without conclusive proof in either case. Inasmuch as the number of recoveries among the controls was small and the number of fatalities in the dibenamine group was even

less, median values are used for presentation. It will be noted that there is a wide variability in the range of bleeding volumes in each category.

Particular attention is directed to a comparison of the bleeding volumes for the dogs which recovered in the control and "test" series. (a) The IBV values in the two groups are essentially identical. This indicates the close approximation of the intensity of impending shock developed in both groups. It was noted that the control survival dogs generally continued to bleed into the reservoir bottle during the first 70 minutes of the hypotension period as their hematocrits progressively decreased. Consequently the SBV was considerable in these 6 dogs (15.9 ml./Kg.). During the final twenty minutes, the bleeding volume tended to remain at status quo, any significant exchange of blood between the dog and the reservoir being an exception rather than the rule. Hematocrit values remained at status quo during this interval. The ARV (2.7 ml./Kg.) in these 6 dogs was small. (b) SBV trends among the dibenamine group were far more variable. This may be related partially to the variable effectiveness of the dibenamine in the different dogs. That the SBV trend should be different from that seen in control dogs would be anticipated, since dibenamine influences vascular mechanisms which ultimately influence bleeding volumes. Hence the SBV among these "test" dogs is definitely less amenable to group consideration. It may be said that in these 18 dogs, bleeding into the reservoir bottle occurred during the first 40 minutes of the hypotension period. Then a 30 minute period of status quo or negligible interchange of blood between the animal and the reservoir was usually observed. During the remaining 20 minutes, blood began to be slowly (automatically) reinfused into the animal from the reservoir. In fact, the ultimate degree of reinfusion, as indicated by the ARV values, parallels or exceeds that seen in the fatalities of the control series (7.1 and 6.8 ml./Kg., respectively). In previous studies, an ARV of 4.0 ml. per Kg. or above in untreated dogs appeared to afford a reliable criterion for the diagnosis of existing irreversible shock. Such a value is obviously not prognostically significant in dibenamine treated dogs.

It is not surprising to observe a considerable ARV in these dibenamine animals. In fact, an ARV in excess of the one obtained (median) was anticipated, since any diminution in the degree of vasoconstriction must entail a considerable enlargement of the total vascular capacity. A priori, the established hypotensive arterial pressure level could presumably only be maintained by proportionate augmentation of the circulating blood volume. Though un-

TABLE 3.—*Bleeding Volumes in ml./Kg.*

		Control		Dibenamine	
		C.R.(6)	F.(14)	C.R.(18)	F.(2)
IBV	Median	35.2	35.0	39.4	
	Range	*29.1–50.4*	*20.0–48.0*	*29.5–49.7*	*36.4 & 46.1*
MBV	Median	55.5	45.7	47.5	
	Range	*44.7–66.6*	*29.1–54.9*	*37.9–70.6*	*53.4 & 56.2*
N-TBV	Median	52.8	36.5	43.5	
	Range	*38.5–61.4*	*20.7–44.5*	*23.4–63.1*	*42.0 & 50.8*
SBV	Median	15.9	10.2	9.0	
	Range	*7.2–28.0*	*0.7–18.2*	*1.9–18.7*	*10.1 & 17.0*
ARV	Median	2.7	6.8	7.1	
	Range	*0–6.2*	*2.3–18.7*	*0–14.6*	*5.4 & 11.4*

C. R. (6) = 6 complete recovery dogs.
F. (14) = shock fatalities.
C. R. (18) = 18 complete recovery dogs.
F. (2) = 2 shock fatalities.
For discussion of IBV, MBV, N-TBV, SBV, and ARV, consult the text.

likely, this increment could be achieved solely by automatic reinfusion of a sufficient volume of blood. It does not seem likely that this was the case with the small and late reinfusion noted. The possibility should not be overlooked that part of the compensatory increment in blood volume was achieved through increased auto-infusion of tissue fluids, through the opening up of previously constricted vascular areas. Such a translocation of tissue fluid should be reflected by further reduction in the hematocrit. In several instances, the hematocrit changes provided support for this possibility. In most of the "test" dogs, however, such a tendency for a reduction in hematocrit was masked or balanced by the automatic reinfusion which tended to elevate hematocrit readings. In general, hematocrit changes were too variable to provide a means of estimating trends. It seems worth emphasizing that any augmentation of the blood volume through reduced vasoconstriction and the establishment of more favorable conditions for autoinfusion of tissue fluids must lessen the volume of blood which had to be automatically reinfused to maintain arterial pressure at a constant hypotensive level.

Inasmuch as previous studies by others as well as by the authors have indicated that liver function is greatly impaired by prolonged hemorrhagic hypotension, an attempt was made to measure liver function before and after the hemorrhagic hypotension period. At the time these experiments were performed (1946) liver function tests for the measure of hepatic metabolism in intact animals were even less satisfactory than they are at present. The bromsulfalein test was selected as most practical for these experimental conditions. It was reasoned that any severe deficiency in hepatic excretory performance in this instance would be suggestive of simultaneous impairment of hepatic metabolic functions. These tests did not prove very satisfactory but they did suggest a trend deemed worthy of mention. Control bromsulfalein tests were usually run the day previous to the hemorrhagic experiment. These proved uniformly normal. The test was again run immediately upon completion of reinfusion. Also, if the animals survived they were repeated during the succeeding 2 to 3 days.

Among the dogs in both groups which entered irreversible shock and died, the findings were consistent in that they indicated high retention of the dye 45 to 60 minutes after its injection (32 to 63 per cent retention). Among the dogs which recovered in both groups, the pattern was definitely less consistent. Many survivals exhibited insignificant retention of dye. In others it ranged from 5 to 38 per cent, falling off to almost no retention when tests were repeated on succeeding post-hemorrhage days. From these studies, the impression was gained that in the dibenamine treated dogs, the degree of hepatic impairment achieved was certainly less than among control dogs and small enough to prevent the onset of extensive irreversible liver damage during the hypotension period. It is recognized, however, that the degree of hepatic congestion and excretory insufficiency cannot be conclusively estimated on the basis of dye retention tests.

Discussion

In two previously reported investigations, using the same standardized hemorrhagic hypotension procedures for inducing the shock state, large doses of dibenamine (15 to 20 mg. per Kg.) were administered (a) 30 minutes and (b) 20 hours prior to the onset of hemorrhage.[5] In the former group, the mortality rate was as great as that seen among untreated control dogs. In the latter series, in which more time was allotted for compensation of the cardiovascular influences of the dibenamine before hemorrhage was begun, tolerance to the hemorrhagic stress was greatly enhanced. In this situation, 70 per cent of the untreated control dogs as compared to 40 per cent of the dibenamine treated dogs entered the irreversible shock state and succumbed. In the present study it was demonstrated that when small doses of dibenamine (3 mg. per Kg.) were administered after impending shock was well advanced, even greater tolerance to the bleeding procedure was achieved. This is demonstrated by the fact that 70 per cent of the untreated control dogs entered irreversible shock as compared to only 10 per cent mortality among the dibenamine treated animals. This small mortality rate occurred in spite of the fact that the bleeding volumes among the dibenamine treated dogs in this present series

were considerably greater than those obtained in the dibenamine treated dogs of the two previous studies in which mortality rates were quite high.

In seeking to answer why greater protection and percentage survival were afforded the dogs in the present series, one can only speculate. It would seem reasonable to assume that the smaller doses of dibenamine did not burden compensatory vascular mechanisms as severely as did the larger doses employed in the earlier studies. This would provide a greater margin of compensatory reserve for counteracting the effects of hemorrhagic hypotension. Undoubtedly, any toxic manifestations of dibenamine were less severe in the animals which received the smaller doses.

It is of even greater interest to attempt an explanation for the fact that only 10 per cent of the dibenamine treated dogs in the present series as compared to 70 per cent of the untreated controls succumbed in *irreversible* shock. The authors are convinced that both groups of animals were exposed to impending shock of the same degree of intensity. There was considerable reason for believing that the dibenamine reduced the degree of existing vasoconstriction shortly after it was administered. Automatic bleeding from dog to reservoir ceased about 10 to 15 minutes after dibenamine was administered, whereas it continued for approximately 70 minutes in the control animals. Following about 20 minutes of status quo, there was considerable automatic reinfusion into the dibenamine animal as indicated in the ARV and the reduction of the MBV and the N-TBV. This was presumably necessary to maintain the hypotensive level in the face of diminution of the peripheral vasoconstriction and the accompanying increase in the capacity of the total vascular bed. The further decrease in the hematocrit seen in a few dogs following dibenamine administration would further substantiate the belief that previous nonpatent vascular channels had been reopened to the circulation. Remington and his co-workers[7] in a somewhat similar series of hemorrhagic shock studies, found the beneficial influences of dibenamine upon survival rates to be associated with lower vasomotor resistance values and higher blood flow values. These are not strictly comparable since the studies were conducted on anesthetized dogs and no attempt was made to sustain any fixed degree of hypotension. Finally, the partial reduction of the blood pressure response to strong pressor doses of adrenaline with occasional small adrenaline reversals obtained in our dibenamine treated dogs adds further strength to the belief that the much greater survival rate is definitely related to improved peripheral blood flow at the given hypotensive blood pressure level. The improvement in blood flow could only be attributed to reduced vasoconstriction, since arterial pressure was maintained at a constant level.

The long accepted belief that severe exsanguination induces intense and widespread vasoconstriction has been conclusively demonstrated by Zweifach and Chambers.[1, 2] It was learned from Freeman and his associates[8, 9] that total sympathectomy affords protection against prolonged vasoconstrictive reduction in tissue blood flow. Considerable emphasis has been placed upon disturbances in renal and hepatic function following severe hemorrhage.[10–12] More recently Chambers, Zweifach and Shorr[13, 14] supplied specific evidence that the kidneys and liver release vasotropic substances when, as a result of hemorrhage, the blood flow to these structures is impaired. As the severity of impending shock increases, greater releases of VEM from the kidneys into the circulation render metarterioles more and more hyperresponsive to vasoconstrictor influences of both humoral and neurogenic origin. Perhaps one effect of dibenamine was to reduce the degree of vasoconstriction in renal arterioles, thus permitting a reasonable degree of renal blood flow at blood pressure levels which ordinarily abolish renal blood flow completely. Under such conditions, less VEM would be released by the kidneys, which would tend to reduce the overall degree of vasoconstriction in the peripheral vascular system and thus permit more satisfactory peripheral blood flow during the drastic hypotensive period. It is also possible of course that the dibenamine may have afforded protection to the metarterioles of large peripheral vascular beds against sympathogenic vasoconstrictor influences of either neurogenic or humoral origin.

The possible improvement in blood flow af-

forced at hypotensive blood pressures by dibenamine action is probably not restricted to any one vascular area such as the kidney. One would expect that hepatic flow, for instance, might be equally improved. Selkurt's studies revealed[15] that hepatic flow is greatly reduced in hemorrhagic states, leading to severe portal congestion. Also, the direct relation between the impairment of liver flow and function and the onset of irreversible shock has been clearly demonstrated by Frank, Seligman and Fine.[12] According to Shorr and Zweifach,[14] such impairment leads to progressively greater release of VDM from the liver, which renders the metarterioles hyporeactive or unresponsive to sympathogenic vasoconstrictor agents. The ultimate and terminal consequences are widespread dilatation of metarterioles and precapillaries with consequent pooling of blood within the many now patent capillaries. Any improvement in hepatic flow through reduction of arterial or even hepatic vein constriction would militate against the production and release of VDM.

From the more practical, clinical viewpoint, however, several points should be stressed. It is difficult to visualize the clinical condition of hemorrhagic shock in which it would be safe or advantageous to employ dibenamine. Rapid restoration of blood volume in itself relieves a situation of prolonged compensatory vasoconstriction. It is felt, however, that this study emphasizes the advisability of preventing the existence of severe prolonged vasoconstriction prior to such time as infusion measures can be instituted. It certainly renders clear the dangers inherent in the prescription of vasoconstrictor drugs for patients in the impending shock state. Such a procedure may be just enough to initiate the transition from the impending to the irreversible shock state.

Summary

Near the middle of an experimental *impending hemorrhagic shock* period, dogs were given small doses of dibenamine, calculated to be just sufficient to produce partial block of sympathogenic vasoconstrictor mechanisms. It was noted that the animals so treated tolerated the standard experimental hemorrhagic hypotension period far better than a series of untreated control dogs. The possible explanations for the improved tolerance has been discussed.

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Changes in the Ballistocardiogram after Exercise in Normal and Abnormal Subjects

By DONALD H. MAKINSON, M. R. C. P.

Ballistocardiograms were taken before and at intervals after mild exercise. The normal response has been ascertained by a statistical study of results obtained on 40 healthy subjects. The response of patients varies widely; in some the change after exercise is much diminished, but in others the response is abnormally increased. In some the form of the ballistocardiogram, normal at rest, becomes abnormal after exercise, so the exercise test will often bring out abnormalities not detected by observations made at rest. Additional evidence was secured that the ballistocardiogram may become abnormal before the clinical picture of coronary heart disease develops.

PHYSICIANS for centuries have been striving to secure objective means of assessing cardiac function by examining the heart during or after exercise. A full account of these is contained in Master's paper on "The Two-Step Test of Myocardial Function."[1] In recent years the ballistocardiograph[2] has made available further evidence of abnormalities in many persons with diseased hearts.[3-7] Hitherto this test has been applied almost solely to resting subjects and it seemed reasonable to expect that an even more delicate test would be secured by obtaining these records while the heart was subjected to a strain, as a slightly diseased heart might be able to behave normally when the body was at rest, but be unable to cope with the situation in a normal manner when increased work was demanded of it. As subjects must not move while ballistocardiograms are being taken satisfactory records cannot be secured during exericse, but they can be obtained immediately after exercise while the heart is still stimulated. Records made at this time and at intervals until the cardiac function returned to normal after exercise have been secured on 98 subjects, 41 of whom were healthy persons, the rest patients from the wards or outpatient departments of the University Hospital. From the results obtained on the healthy group normal standards have been developed, largely by statistical methods When the results obtained on the patients are compared with these normal standards it is clear that evidence of cardiac dysfunction can be readily secured by this exercise test, and that abnormalities not identified by records obtained at rest can be demonstrated in many instances.

In 1938 a study of this nature was commenced in this laboratory by M. W. Stroud and E. M. Evans,[8] then undergraduate medical students working under Dr. Starr's direction. Later Dr. Starr made a few observations himself but the work was soon abandoned owing to the war. The records obtained in this early work were made available to me and I have remeasured them and recalculated the results. In addition many more subjects were tested, so that the great majority of the tests were conducted by myself in 1948–49. But the old records were valuable because they not only provided independent confirmation of the later results but also permitted me to secure long after-histories on some of the more interesting cases.

METHODS

Subjects

A total of 98 exercise experiments was performed upon 41 subjects who considered themselves to be healthy, and 57 who were clinically abnormal. The control group was drawn from medical students, faculty members and hospital employees. Their ages and sexes are given in table 1. The 57 patients were secured from the wards and outpatient departments of the University Hospital; all had been subjected to the routine hospital study and these data were employed in assessing their clinical diagnosis and status. Thirty-eight were males, 25 fe-

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males, and they can be subdivided as is shown in table 4.

The 13 patients included in the rheumatic heart disease group consisted of 8 with rheumatic mitral disease alone, none of whom had ever been in congestive failure. Four of these, aged 20, 41, 20 and 30, all in Functional Class I, had mitral stenosis alone and were not receiving digitalis. Two, aged 38 and 52, who had auricular fibrillation in addition to mitral stenosis, were receiving digitalis and they were placed in Functional Classes II and III, respectively. In 2 further patients, aged 25 and 27, placed in Functional Classes II and III, mitral stenosis was associated with mitral incompetence. Of the remaining 5 patients, one, aged 34, in Functional Class I, had mitral stenosis and aortic stenosis; two, aged 20 and 30, in Functional Classes I and II, had mitral stenosis and aortic incompetence; and two, aged 20 and 21, in Functional Class I, had pure aortic incompetence.

None of the 9 patients with the anginal syndrome, whose ages ranged from 47 to 77, gave a clinical history of myocardial infarction, although one individual showed electrocardiographic changes suggestive of an old posterior myocardial infarct.

TABLE 1.—*Distribution of Normal Subjects with Regard to Age and Sex*

	Age in Years					
	20–29	30–39	40–49	50–59	60–69	Total
Males	12	4	5	5	4	30
Females	9	2	0	0	0	11

The 4 patients with essential hypertension, aged 34, 51, 56 and 67, had blood pressures of 190/125, 150/100, 190/110 and 170/105 when at rest. None of these had evidence of renal involvement nor had they been in congestive failure. One, however, a man aged 51, showed electrocardiographic evidence of left bundle branch block.

The 2 patients with thyrotoxicosis had basal metabolic rates of +58% and +62% and neither showed any disturbance of heart rhythm, nor was there other evidence of thyroid heart disease.

The 11 cases of neurocirculatory asthenia were characterized by complaints related to the circulation, especially dyspnea on exertion and precordial pain not definitely related to exertion, but extensive hospital studies failed to reveal any evidence of organic disease.

The 3 patients with postural hypotension were aged 44, 44 and 38; they experienced symptoms of vertigo and faintness associated with a fall in blood pressure on assumption of the erect posture. One of these cases has been described in detail.[9] Incapacity of the other two was not so great.

The 3 patients with hypothyroidism were aged 43, 35 and 52; they had basal metabolic rates of −10%, −36% and −20%, respectively.

The miscellaneous group consisted of 2 cases of traumatic A-V fistula and single cases of pheochromocytoma, syphilitic aortic regurgitation, Addison's disease, arteriosclerosis, emaciation (cause unknown), postoperative thyroidectomy with bundle branch block, tetrology of Fallot, diabetes mellitus, polycythemia vera and coarctation of the aorta.

Technics

All subjects were examined more than two hours after their last meal and ballistocardiograms were taken according to the usual technic, after a fifteen-minute rest period. Mild exercise was performed on the Master steps, 2 steps each of 9 inches, arranged so that the top step has a lower step on each side of it. The number of trips across the steps was graded according to age and weight. Half the number of trips recommended by the Master tables[1] were performed in half the time allotted by him, so my subjects took from 9 to 12 trips across the steps in forty-five seconds.

The first ballistocardiogram was secured after fifteen minutes' rest in the horizontal position. The subject then arose and walked over the steps. At the completion of the exercise he immediately lay down and a ballistocardiogram was taken as soon as possible. This was usually about ten seconds after cessation of exercise but the extremes were five and thirty seconds. Additional records were secured at 50, 90 and 180 seconds after completion of exercise. Figure 1 gives several typical examples of the records secured.

Blood pressure was estimated at rest and in the intervals between the taking of ballistocardiograms after exercise.

Analysis of the Records

When the record was normal in form typical large and small complexes were selected and measured. Cardiac output was calculated according to the following formula[15]:

$$\textit{Percentage deviation from normal} = K\sqrt{2\int Idt + \int Jdt}\,\sqrt{c} \times \frac{\textit{Pulse rate}}{\textit{Body weight}} - 100$$

$\int Idt$ and $\int Jdt$ being the areas of the I and J waves of the ballistocardiogram in mm. sec. and c the duration of the cardiac cycle in seconds, and K being obtained from Starr's table.[15] The ballistocardiogram was adjusted so that 280 Gm. displaced the light spot 1 cm.

The effect of exercise on the circulation was estimated in the following way which is best made clear by an example. Subject EWC, after fifteen minutes' rest, had a circulation which was −21% below the mean value of healthy resting subjects,

age and weight being considered. At 10, 50 and 90 seconds after exercise his circulation deviated by +40%, +1% and −16% from the same mean value of healthy resting subjects. Therefore, the changes due to exercise were recorded as +61%, +22% and +5%. Data so calculated were averaged and the results appear in table 2 which defines the normal standards.

After all my experiments had been completed, a method for the estimation of cardiac strength from the ballistocardiogram was published,[11] so it seemed of interest to calculate standards for the normal response to exercise as measured by this new method of assessing cardiac function. Accordingly the depth and altitude of the I and J waves of typical large and small complexes of the respiratory cycle were measured for all subjects both before and after exercise; the sum of these four measurements was compared with the expected resting value for each subject, calculated from a regression formula. The deviation of each estimation from the expected resting value was expressed in per cent and the changes due to exercise were calculated as in the example cited in the preceding paragraph. The results have been placed in table 3.

TABLE 2.—*The Normal Response to Mild Exercise Expressed as Changes in Cardiac Output*

Time after Exercise	No. in Group	Changes in cardiac output after exercise*	
		Mean	Standard Deviation
sec.		%	%
5-30	40	+47.4	24.2
50	40	+14.25	14.3
90	40	+4.87	10.56
180	40	+3.97	11.1

* Differences between the resting cardiac output of each subject before exercise and the values found after exercise.

TABLE 3.—*The Normal Response to Mild Exercise Expressed as Changes in the Strength of the Heart*

Time after Exercise (Sec.)	No. in Group	Changes in cardiac strength after exercise*	
		Mean	Standard Deviation
		%	%
5-30	40	+44.7	29.7
50	39	+20.2	22.5
90	39	+13.7	16.1
180	37	+8.0	15.5

* Difference between the spread of the complexes ($I_1 + J_1 + I_2 + J_2$) for each subject before exercise and the values found after exercise.

When the record was abnormal in form the method of recording used by Starr and Mayock[5, 10] was adopted. First the proportion of abnormal complexes present was estimated, and second the abnormalities of form of the complexes were described in detail. But in order to simplify this presentation, the records have been classified merely as normal or abnormal. The estimation of cardiac output was not attempted if the ballistic form was abnormal. However, if only one complex in each respiratory cycle was abnormal, the cardiac output was calculated from a representative small normal complex and a representative large complex, in the usual manner.

The statistical analysis was performed according to the methods of Fisher.[12] The word significant will be used only in the statistical sense, indicating a probability of 95 in 100 or over that the result was not due to chance alone.

RESULTS

Results Secured on Healthy Persons. A statistical analysis of the response to exercise of all members of the normal group failed to reveal any significant correlation with age or sex and so the group was analyzed as a whole. Table 2 gives the results of this analysis. Immediately after exercise had ceased the cardiac output was found to average almost 50 per cent above the resting level. This increase subsided rapidly so that the resting value was almost, but not quite, attained at 180 seconds after exercise had ceased. We propose to regard as abnormal any case which deviates from the mean by more than twice the standard deviation.

Average Results Secured in Various Types of Disease. Table 4 gives standard deviations for the increase in cardiac output after exercise obtained both in the normal group and in the clinically abnormal cases grouped according to the chief diagnosis. The averages show that an increase in cardiac output after exercise, significantly greater than normal, was found in patients with rheumatic heart disease during the first ninety seconds after exercise had ceased. In those with neurocirculatory asthenia the average increase of circulation immediately after exercise was very close to the normal, but the increase was much more prolonged, becoming significantly greater than the normal at fifty seconds. Both cases with thyrotoxicosis showed increases after exercise which far ex-

ceeded the average normal at each test made during the first ninety seconds after exercise, but because of the small number tested statistical significance was attained at only one of the three estimations.

In angina pectoris the average increase immediately after exercise was very close to the normal but increased cardiac activity persisted much longer. At fifty seconds after exercise the mean was significantly higher than normal and for the rest of the test the difference in the averages is striking even though statistical significance was not quite attained. An analysis of the individual results is given in table 5, and shows that 4 of the 9 cases did not have an excessive increase after exercise; however, no significant clinical differences could be found between those who did and those who did not show an abnormal increase in cardiac output.

In contrast, the cases of hypothyroidism, postural hypotension and essential hypertension, judging by the means of each group, responded to the exercise by a smaller increase than the normal which was significant at the first test in all three groups.

The failure of the 4 cases of hypertension to increase their circulation after exercise is especially striking and indeed the whole pattern of their response is abnormal, the mean diminishing until it reaches a point not only significantly below the normal, but also 27 per cent below the average attained before exercise.

Results in Individual Patients. The normal standards permit testing the normality of individuals as well as of groups, so all the 57 members of the abnormal group have been thus tested. This has been done in two ways, by studying the changes of estimated cardiac output after exercise, and by neglecting the values found before exercise and concentrating attention on the levels obtained after it. When the change due to exercise was studied and the findings in each patient compared with the normal range, defined as the mean value ± twice the standard deviation, it was found that 28 of the 57 patients gave an abnormal response to exercise. In 9 of these the circulation increased less, in 19 it increased more than normal after exercise.

The level of the circulation after excercise was of great interest because in this step-climbing test the work performed was automatically adjusted to the size of the subject. Therefore it seemed that useful information might be obtained by neglecting the resting value as irrelevant and concentrating attention on the level of the circulation after exercise. Accordingly the data have been analysed from this viewpoint and table 6 shows the results of the statistical analysis for both the normal and the abnormal groups. The same trends for specific clinical groups are noted in this analysis as in the previous one (Table 4), except for the neurocirculatory asthenia group which shows

TABLE 4.—*Average Change of Cardiac Output after Exercise from Each Subject's Resting Value*

Group	No. of Subjects	Time After Exercise							
		5–30 secs.		50 secs.		90 secs.		180 secs.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
		%	%	%	%	%	%	%	%
Normal	41	47.4	24.2	14.25	14.3	4.89	10.56	3.97	11.1
R.H.D.	13	73.4*	43	34.8*	30	13.3*	16.6	7.8	18.2
Angina	9	48.8	27.4	31.5*	31.4	13.4	26.1	6.1	18.1
N.C.A.	11	49.7	71	24.7*	55.5	8.0	11.8	1.5	9.25
Thyrotoxicosis	2	58	37	24.5	14.5	21.5*	19.5	−6.5	3.5
Hypothyroid	3	15.9*	16.4	19	24	10	17.9	4	15.64
Postural Hypotension	3	37.3	4.5	11.3	2.4	1.3	13.1	4	10
Hypertension	4	2.5*	22.2	2.5	23.4	−9	9.3	−27*	32.9
Miscellaneous	12								

* Denotes statistically significant difference from corresponding value in normals as determined by Fisher's "t" test.

TABLE 5.—*Changes after Exercise in Patients with Angina Pectoris*

Age	Functional Class	Cardiac Output (Resting)	Cardiac Output Change from resting values at times from 5 to 180 sec. after exercise			
			5–30 sec.	50 sec.	90 sec.	180 sec.
years		%	%	%	%	%
64	III	−22	59	0	−19	−12
49	II	−13	64	23	−8	7
54	III	36	40	−3	11	—
77	III	−11	71	53	30	−4
47	II	−14	12	5	−2	−23
66	III	−5	19	20	−11	−18
53	III	−17	48	53	54	27
47	II	−2	27	27	8	0
59	II	5	57	63	15	−7

mean levels of cardiac output during the whole period after exercise which are less than those for the normal group.

When the normal range of levels after exercise, defined as the mean value ± twice the standard deviation, is compared with the individual results of the abnormal group, 14 of the 37 persons in this group gave an abnormal response. These 14 subjects are included in the 28 so found when the increase of the cardiac output after exercise is considered (Table 4).

Changes of Form of the Ballistocardiographic Curve After Exercise. In addition to abnormalities of the response to exercise detected by abnormal changes in size of the record, and of the cardiac output as calculated from it, the exercise test often gave evidence of abnormality of another kind. In the group of clinically abnormal subjects, 40 had normal tracings at rest and in 12 of these the form became abnormal after exercise. Examples are shown in figure 1 B and C. In 13 of the 17 patients who had abnormal tracings at rest, the abnormality persisted after exercise as one would expect, but it was a surprise to find that in 4 the tracings became normal in form after exercise. Twenty-eight of the clinically abnormal group gave an abnormal cardiac output response to exercise and of these, 18 had normal curves before, 3 of which became abnormal after exercise and 10 gave abnormal curves before, 3 of which became normal after exercise.

TABLE 6.—*Average Levels of Cardiac Output after Exercise in Terms of Average Normal Resting Values*

Group	No. of Subjects	Time After Exercise							
		5–30 secs.		50 secs.		90 secs.		180 secs.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
		%	%	%	%	%	%	%	%
Normal	41	43.8	29	10.4	17.6	2.96	19	0.16	18.1
R.H.D.	13	67.5	35.8	25.1*	26	6.5	22.6	1	20.4
Angina	9	44.1	19.7	26.7*	23.2	8.6	21.3	−3.7	15.7
N.C.A.	11	33.1	34.2	0.1	27.6	−12.4	23.8	−14.6*	38.4
Thyrotoxicosis	2	85	45	56.5*	16.5	53.5*	20.6	2.5	1.6
Hypothyroid	3	8.3*	26.2	11.6	2.14	2.6	7.85	−3.3	9.8
Postural Hypotension	3	23.6	18.9	−2.3	19.3	−12.3	6.9	−9.6	11.9
Hypertension	4	22.7	37.8	17.6	5.51	1.5	11.6	−9.5	12.1

* Denotes statistically significant difference from corresponding value in normals as determined by Fisher's "t" test. All results are expressed as per cent deviation from the average resting normal. In this compilation the resting level of the individuals tested has been neglected.

The commonest abnormality of form produced by exercise was slurring, widening or splitting of the J wave; this was always found in the first tracing taken after exercise, and the form usually had returned to normal by 180 seconds after exercise had ceased (Fig. 1, B and C). In a few cases the I wave became small soon after exercise, returning to normal later.

Blood Pressure and Pulse Rate Responses. In his experiments, employing the full number of recommended trips, Master found that the blood pressure (systolic and diastolic) and the pulse rate of the majority of his normal subjects had returned to the resting value within two minutes of the cessation of exercise. In the 98 subjects in this series who performed half

the number of trips required by the full Master test, 14 of the clinically abnormal and 5 of the clinically normal failed to have a return of their blood pressure and pulse rate to within 10 points of the resting value within two minutes after exercise.

TABLE 7.—*Changes after Exercise in Patients with Rheumatic Heart Disease*

Age	Functional Class	Resting Cardiac Output	Percentage increase in Cardiac Output over resting values at times from 5 to 180 seconds after exercise				
			5–30 sec.	50 sec.	90 sec.	180 sec.	
		%	%	%	%	%	
Mitral Stenosis Alone							
30	I	−14	43	19	7	8	
20	I	20	77	27	24	9	
41	II	−24	24	28	−1	−1	
20	II	−29	155	42	7	8	
38	II	−32	88	43	26	16	Auricular
52	III	−19	51	16	13	9	Fibrillation
Mitral Stenosis and Mitral Incompetence							
25	I	−20	75	8	1	−14	
37	III	−35	149	131	39	39	
Mitral Stenosis and Aortic Stenosis							
34	I	7	53	31	16	15	
Mitral Stenosis and Aortic Incompetence							
20	I	11	15	9	0	4	
30	II	−5	62	39	47	38	
Aortic Incompetence							
21	I	42	41	19	−20	−34	
20	I	11	121	41	15	5	

Discussion

It was the purpose of this investigation to determine whether a study of ballistocardiographic tracings taken after mild exercise would help further in distinguishing patients with abnormalities of cardiovascular function. It is believed that this object has been achieved but a difficulty has been encountered which must not be minimized. The results obtained in healthy subjects scatter so widely that only marked abnormality can be detected. Much thought has been given to the reasons for this diversity of normal response.

The scatter of the response to exercise in healthy persons is greatly increased by the fact that some subjects give results of a pattern different from the majority. In most subjects, as one would certainly expect, the maxima for both cardiac strength and output were found immediately after exercise was over and the values declined slowly for the rest of the period of observation. But some apparently healthy persons responded in an entirely different manner. Thus there were three cases in which the maximum values were not attained until 90 or even 180 seconds after the cessation of exercise. Another subject, apparently in excellent physical condition but 54 years old, gave an even more unusual response. He always had resting values considerably larger than the average for his age and after the mild exercise required in this test, he manifested little if any increase. This subject was tested repeatedly, always with the same result. Perhaps in view of his unusually large circulation at rest no increase was needed for such mild exercise, a viewpoint in accord with another observation made on him. When this subject stood upright his resting circulation was much smaller than when he lay supine. When given an exercise test with ballistocardiograms taken in the upright position, his circulation increased normally after exercise. But one of Hickam and Cargill's[14] subjects, judged to have a normal circulation although suffering from syphilis of the central nervous system, also had an insignificant increase in cardiac output after mild exercise although his resting circulation was not unusually elevated. So perhaps a certain percentage of healthy persons react to mild exercise mainly by increasing their arteriovenous oxygen difference. But whatever the reason for these divergent responses among healthy persons, the inclusion of their data has greatly increased the normal range and rendered the detection of abnormality more difficult.

Several attempts were made to diminish the scatter of the normal group and so to improve the ability to detect abnormality. Normal standards were made in terms of cardiac strength[11] and of the level of estimated cardiac output after exercise, but the results disclosed a scatter as great as or greater than that of the changes of cardiac output after exercise. So no means of reducing the scatter of the normal standards has been found. However, despite

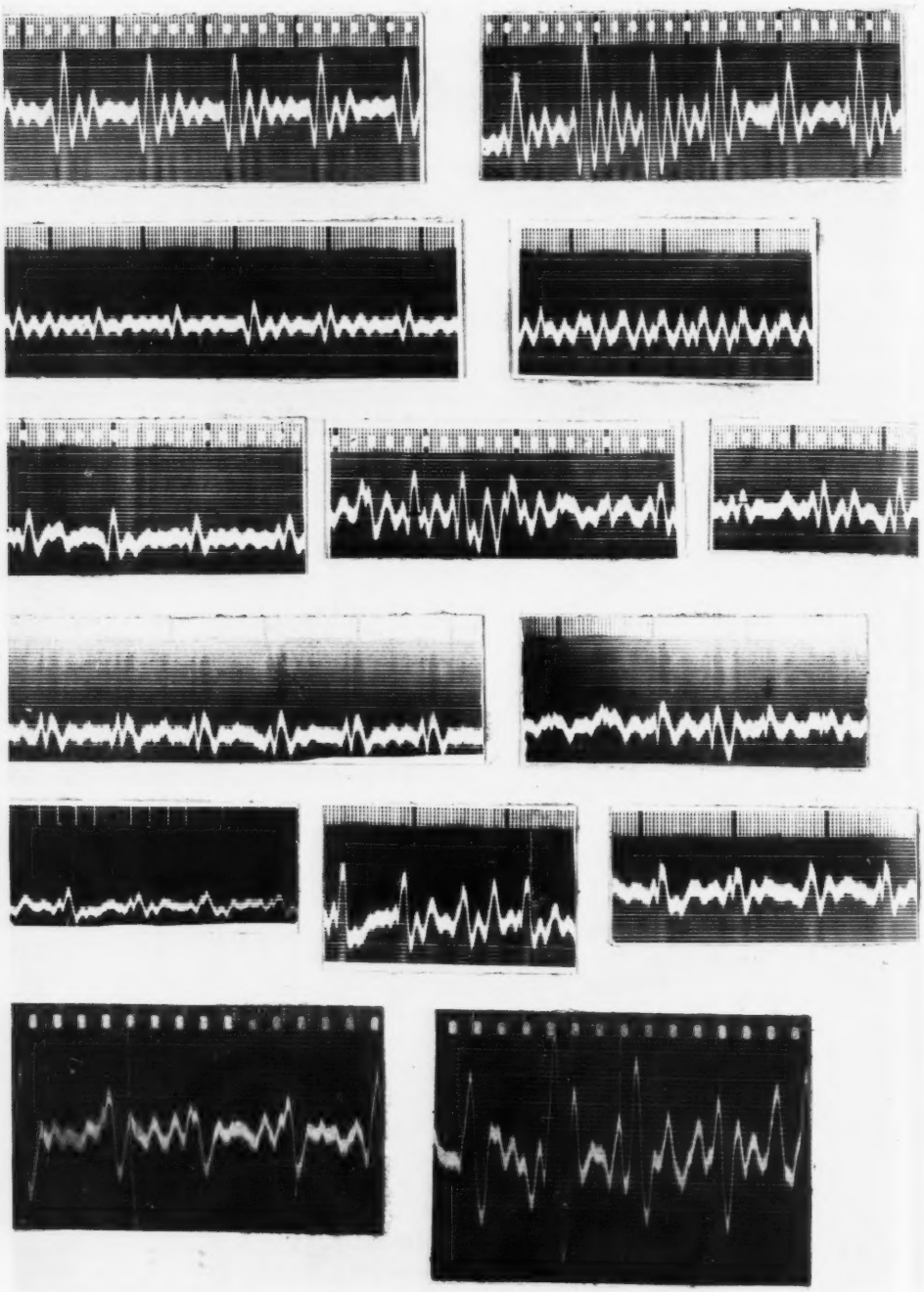

FIG. 1

this situation, the abnormalities found in many patients are so great that they may be readily detected by the ordinary statistical criteria and it seems evident that the exercise test provides evidence of an abnormality undetected by other methods in many cases.

It will be recalled that ballistocardiograms taken *at rest* may detect abnormality in one of three ways. The record may be too large or too small for a subject of that age and weight, abnormalities usually identified by calculating cardiac output from the wave measurements, or the record may be abnormal in form. Ballistocardiograms taken *before and after exercise* may also be used to detect abnormality in three additional ways; first, after exercise the normal increase in size of the record and in the calculated cardiac output may not take place; second the cardiac response to exercise may be excessive; or third, the form of the record, normal before exercise, may become abnormal after it.

The results clearly indicate that the exercise test is the more delicate. Thus, among my 98 subjects, tests made at rest indicated that 18 subjects showed abnormality by abnormal change in cardiac output, 17 by abnormal shape of the ballistocardiogram, and 7 in both ways. In the records made after exercise 28 were judged abnormal on the basis of abnormalities of form of the curve not present at rest, and 4 on the basis of both. Thus 28 individuals were picked out as abnormal from the resting ballistocardiographic tracing and 23 additional subjects, whose ballistocardiogram passed as normal at rest, had abnormal ballistocardiographic tracings after exercise. Consideration of the absolute cardiac output after exercise, instead of the increase over resting cardiac output, does not increase the usefulness of the test. Experience with the estimation of cardiac strength is as yet insufficient to form a basis for opinion.

This investigation was designed with the expectation that cardiac abnormality, not to be identified at rest, would be made manifest because a diseased heart would be unable to increase the cardiac output after exercise or, in an effort to do so, would contract in an abnormal manner which would result in distortion of the ballistocardiogram. These expectations have been fully realized in many instances. In my cases of myxedema and essential hypertension the failure to increase the size of the ballistocardiogram after exercise was often conspicuous; Hickam and Cargill[14] found a similar failure to increase cardiac output after exercise in cases of congestive failure. In addition typical examples of the many instances in which abnormality of ballistic form developed after exercise are given in figure 1.

FIG. 1. Ballistocardiograms taken before and after exercise. The reproduction from A to E inclusive is 3/5 actual size; that of *F* is 4/5 actual size. Time records largest interval = 1 second.

A. Records on D. H. M., a healthy man aged 28, height 6′0″, weight 160 lbs. *Left* before exercise, *right* commences 10 sec. after the cessation of exercise. This response is typical of normal subjects.

B. Records of J. C., 49, 5′2″, 107 lb. Taken in 1939 when she was in the hospital ward because of a gastric complaint. The routine study gave no evidence of cardiac disease at that time and none was suspected by the attending physician. *Left* record before, *right* record 10 sec. after exercise. Note that the amplitude does not increase after exercise and the form becomes abnormal.

C. Records of J. C. who now has developed angina pectoris, taken in 1949. *Left* record before, *center* 10 sec. after, *right* 240 sec. after exercise. Note that the record taken at rest is still normal, the record taken immediately after exercise is abnormal in form but of increased amplitude. The abnormality disappears by the time of the last record.

D. Records of D. R., aged 47, 5′3″, 163 lb., a case of angina pectoris. *Left* record before exercise, *right* at 10 sec. after exercise. Both tracings are abnormal but there is very little increase in amplitude of the complexes after exercise.

E. Records of S. S., aged 48, 5′4″, 131 lb., a case of neurocirculatory asthenia. *Left* record before exercise, *right* 15 sec. after exercise. Both tracings are abnormal but there is considerable increase in amplitude of the complexes after exercise.

F. Records of J. B., aged 58, 5′7½″, 132 lb., a case of toxic nodular goiter. *Left* before exercise, *right* 25 sec. after exercise. The records at rest and after exercise are both abnormal in form but the amplitude of the complexes does increase after exercise.

Also not unexpected was the increased response of the cases diagnosed as neurocirculatory asthenia; this is in keeping with the concept[13] that inability to regulate the circulation properly is a fundamental factor in this condition. A similar abnormality in the cases of thyrotoxicosis is consistent with the well known instability of the circulation seen not only in patients but also in experimental animals given large doses of thyroid. The differences from the normal in these 2 cases were large; significance was not attained more frequently solely because of the small number.

But it is characteristic of many investigations that they raise as many problems as they solve. The finding that my cases of rheumatic heart disease and of angina pectoris gave, on the average, an excessive response to exercise came as a complete surprise. So the clinical data were carefully studied to see if this most unexpected finding could be understood or explained away. Table 7 gives the findings secured in the cases of rheumatic heart disease in detail.

It will be recalled that the response to exercise has been measured in terms of the findings at rest, so it was possible that the unexpected abnormality mentioned might be due to a diminished circulation at rest rather than to an unusually high level during exercise. Reference to table 7 shows that this is in part true; 7 of 9 cases without aortic incompetence had resting circulations below the average normal. But careful study of these data shows that this is not the full explanation, for in 3 cases the increase after exercise exceeded 120 per cent and in many other cases the abnormal prolongation of the response is conspicuous.

Another possible explanation deserves comment. In cases of aortic regurgitation the ballistocardiogram measures the true stroke volume, not the amount of the circulation. In this condition an increase in the amount of blood regurgitated after exercise in the presence of a normal increase in circulation after exercise, would cause an abnormal increase in ballistic amplitude. But in only 4 of the 13 cases of rheumatic heart disease was this lesion diagnosed so this is obviously not the explanation for most cases.

A similar study was made of the cases of angina pectoris in my series. The mild exercise asked of these patients was well within their capacity and pain was not induced in any instance. Nothing was found which would explain the finding that their response to exercise tended to exceed the normal, rather than the reverse. Apparently therefore, some cases with demonstrated organic heart disease respond to mild exercise by an abnormal increase in cardiac function, an increase of magnitude, of duration, or of both.

Apparently we are dealing with a real phenomenon which at first thought seems strange, as one would certainly expect a diseased organ to respond to a constant stimulus less actively than a normal one. However, evidence is accumulating that this expectation is by no means always realized. Thus digitalis,[16–18, 22] theophylline ethylene diamine[18, 19] and hypertonic glucose injected intravenously[20, 21] all cause a greater increase in cardiac output, or an increase of longer duration, or both, in persons with diseased hearts than in normal persons. So perhaps one should not be surprised that the same is true of mild exercise; the diseased heart being frequently over-responsive to stimulation and so less well adjusted to the demands which may be put upon it. And this finding is in support of the old clinical conception that "functional" heart disease is a common complication of organic heart disease.

Equally puzzling is the finding, in 4 patients, that ballistocardiograms abnormal in form during rest either improved or became completely normal in form after exercise. Probably this finding is comparable to that described by Starr and Mayock[5] in which certain patients, giving ballistocardiograms abnormal in form while they lay at rest, gave a more normal record after they arose and stood upright. It is hard to think of a satisfactory explanation for this finding. It has been suggested that in an early stage of myocardial disease, cardiac weakness might be most apparent when the heart is under no compulsion and so is "taking it easy"; when an increased circulation is demanded, the cardiac reserves of strength are called out and the deficiency overcome.

Mention has been made of the result obtained in the one healthy subject whose circula-

tion, which at rest was at or above the upper normal limit, increased but little after exercise, making him abnormal when judged by the standards in table 2 because the percentage increase was so small. In this case the absolute amount of the circulation after exercise did not differ from that of most normal subjects, so perhaps no increase was needed. This observation stimulated us to study the relation between the absolute amount of the circulation at rest and the percentage increase after exercise. Using all our data (98 cases), there was significant negative correlation between these two values ($r = 0.32$) so that persons with low resting cardiac outputs can be expected to have a greater increase after exercise than those with high resting values. However, when (in an attempt to improve our normal standards) we studied the same relationships for the healthy persons only, the correlation was not significant.

Evidence for a relationship between ballistic abnormalities and coronary heart disease[15] continues to accumulate rapidly. Three of my subjects, tested with the expectation that they belonged in the normal group, because they considered themselves to be healthy and because there were no abnormal clinical findings, were found to have ballistocardiograms which were abnormal in form both before and after exercise. One of these, a man of 62, developed angina pectoris three months after completion of the investigation. The others were both over the age of 55, university professors, and accustomed to indulge in ordinary activity without distress. In one other subject the tracing, normal at rest, became abnormal in form after exercise; he was 42, a coal miner by occupation, and gave no other evidence of cardiac disease.

An interesting case which illustrates the value of taking ballistocardiographic records after exercise is given by the following 10 year after-history.

Case Report. J. C., a 49 year old widow, was admitted to the University Hospital in March, 1939, for investigation of her gall bladder function following an attack of jaundice lasting three months. She had no complaints suggestive of cardiovascular disease at this time, the heart being reported as clinically normal and blood pressure 130/80. X-ray films showed a normal cardiac contour. The electrocardiogram, however, showed low voltage T waves in all leads. A ballistocardiogram taken after exercise at this time (Fig. 1 B) showed that although the tracing was normal at rest, after exercise slurring of the J waves became most noticeable. Her resting cardiac output at this time was −13 per cent. When the tracings were reviewed in 1949 it was decided to attempt a follow-up study and for this purpose the patient was readmitted to the University Hospital in March of that year. On this occasion she gave a history of angina pectoris always precipitated by exertion and relieved by rest. These attacks have been present since 1943. Clinical examination revealed no significant abnormality in any system and the blood pressure was 120/65. A further exercise test (Fig. 1 C) was carried out which again showed a normal resting ballistocardiogram which still became abnormal with slurring of the J waves after exercise. The resting cardiac output was +5%.

The case of J. C. reported above is the first instance of a patient with a ballistocardiogram normal at rest but abnormal after exercise, who has developed coronary heart disease in the years which followed.

Summary and Conclusions

1. Results of the analysis of ballistocardiograms taken before and at intervals after mild exercise in 41 normal subjects and 57 patients, many with various types of heart disease, are presented.

2. Normal standards of cardiac output response after exercise are defined and applied to the results obtained in patients with heart disease.

3. Twenty-eight subjects were found to have abnormal ballistocardiograms at rest. An additional 23, whose ballistocardiograms at rest were normal, gave abnormal tracings after exercise; in a few cases the reverse was true.

4. Patients were encountered who failed to respond to the exercise by increasing their cardiac output, and others showed excessive response to the exercise.

5. It is considered that ballistocardiograms after exercise give additional information on myocardial function which is not obtained by other clinical methods or by the ballistocardiogram at rest.

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The Electrokymograph: Studies in Recording Fidelity

By Harry F. Zinsser, Jr., M.D., Calvin F. Kay, M.D., and J. Malvern Benjamin, Jr., M.S.

Several electrokymographs were subjected to study of their recording fidelity. Distortions were found in respect to *time* and *amplitude* of recorded response. The recording defects were analyzed quantitatively, and the degree to which the various components of the electrokymograph contribute to these distortions was measured. The significance of these deviations in recording fidelity is discussed in reference to the application of the electrokymograph to the study of cardiovascular dynamics.

THE ELECTROKYMOGRAPH was devised to record the border motions of the heart and great vessels.[1–6] Although simple in operation, the instrument is complex in principle. In ordinary fluoroscopy, an x-ray beam, pulsating at 120 cycles per second, passes differentially through the thoracic tissues and causes characteristic shadows and translucencies to appear on a fluoroscopic viewscreen. The process of electrokymography interposes another small rectangle of fluoroscopic screen placed perpendicularly to the moving border of the desired objective. The changes in intensity of illumination of this screen are converted by a photomultiplier tube to changes in millivolt output from the tube. These millivolt changes are recorded by an electrocardiograph after passage through an electrical filter. The filter is a complex system of condensers and resistors, designed to eliminate the 120 cycle per second pulsations of the x-ray beam without interfering with the lower frequency changes in fluoroscopic screen illumination.

As with any apparatus, knowledge of the recording fidelity is essential. Wave motions generated on the fluoroscopic receptor slot might be distorted in each of the several essential components of the electrokymograph: (1) The fluoroscopic screen, (2) the photomultiplier tube, (3) the filter, and (4) the electrocardiographic recorder. Distortions of two general types are possible: Those related to *amplitude* and those related to *time*. This study was designed to determine the amplitude distortion and time lag of the electrokymograph.

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Fidelity of the Electrokymograph in Recording Amplitude

In a previous study,[7] preliminary testing of the electrokymograph showed two major classes of errors in recorded amplitude: (1) Those concerned with the *linearity* of the phototube unit, i.e. the deviations from a constant amplitude of response when a standard stimulus is applied to different areas of the fluoroscopic screen, and (2) those concerned with the *frequency response* of the apparatus, i.e. the deviations from a constant amplitude of response when a standard stimulus is applied at varying frequencies.

Linearity

The electrocardiographic recorder and the filter, as component parts of the electrokymograph, record changes in output of the photomultiplier tube as a linear function of voltage, provided that the frequency remains constant.* However, the phototube unit itself does not convert changes in illumination into millivolt output in uniformly linear fashion. Ideally, the exposure of any unit area of the small fluoroscopic screen of the phototube to an x-ray beam

* This can be demonstrated by applying the output of an oscillator to the input of the filter and to an oscilloscope in parallel. The recorded amplitude from a 2 millivolt stimulus will be found to be twice as great as that from a 1 millivolt stimulus at any given frequency.

of constant intensity should result in a millivolt output from the tube equal to that resulting from the exposure of any other unit area of equal size. If such were the case, the shape and magnitude of the deflections recorded from a moving border would be independent of the position of the shadow of the border on the screen, provided it remained on the screen throughout the cycle. The metal slot which bounds the fluoroscopic screen of each of three commercial phototubes (one of type A, two of type B) was found to be approximately 25 mm. in length. Thus ideally, a zone 18 mm. in length would be available for centering, while recording deflections produced by a border movement of 8 mm. magnitude.

Such ideal uniformity of the receptor zone was found in none of the instruments when the actual linearity of phototube reception was tested as follows: Each phototube was placed in a horizontal position, with the receptor slot lying uniformly in the path of an x-ray beam. Immediately in front of the slot was a sheet of lead into which a vertical slit, 2 mm. in width, was cut. This lead sheet was so mounted that the x-ray beam through the slit could be made to expose any area of 2 mm. width on the reception screen. Since the electrical system would not record direct current output of the photomultiplier tube, it was necessary to obstruct intermittently the entire x-ray beam with a second lead sheet, which was moved back and forth at 0.5 second intervals. The magnitude of the deflections was then recorded as the slit of the first lead sheet was moved in successive 1 mm. steps across the length of the slot of the phototube unit.

The results of measurements so recorded with a phototube of type "A" are graphically illustrated in figure 1, expressed in terms of percentage of the maximum deflection recorded. It will be observed that the magnitude of the response to a given stimulus is highly dependent upon the portion of the receptor screen to which the x-ray stimulus was applied. The response is relatively constant, with a maximum error of 15 per cent, within a zone 9 mm. in length near the middle of the screen. If a maximum error of 30 per cent is tolerable, 14 mm. of screen may be used. Beyond these limits, the error becomes very large. It is also to be noted that the geometric center of the screen, (indicated on the commercial units by projecting metal knobs) is appreciably displaced toward the free end of the tube from the center of the zone of maximum linearity. Similar testing of two phototube units of type "B" gave practically identical results. The centering knobs were likewise displaced about 2 mm. toward the free end of the tube from the center of the zone of maximum sensitivity.

Frequency Response

As reported previously,[7] increased frequency of repetition of a stimulus of fixed magnitude* caused a decrease in the amplitude of the resultant electrokymographic tracing. The essential components of the electrokymograph contribute in varying degrees to this total effect. Studies were undertaken (1) to demonstrate the frequency response characteristics of each of these components, and (2) to show the effects on cardiovascular wave forms of these response characteristics. Various electrokymographs

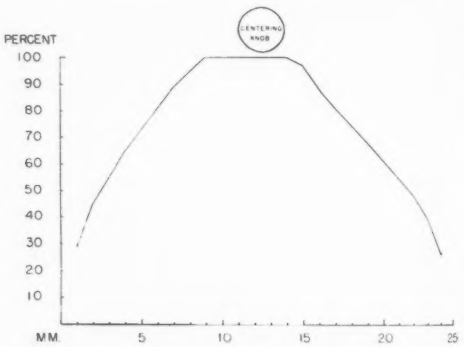

FIG. 1. The sensitivity of various portions of the receptive slot of the phototube in terms of the percentage of maximum sensitivity.

* The standard stimulus consisted of a wave generated by the rotation of a circular lead disk mounted eccentrically on the shaft of a variable speed motor. The x-ray tube, lead disk, and phototube are aligned (with the phototube receptor slot perpendicular to the edge of the disk) in a manner such that the x-ray beam falling on the phototube is interrupted by the edge of the rotating lead disk. For practical purposes the resultant wave closely approximates a pure sine wave.

were tested, including noncommercial and commercial types. In studying the frequency response effects of the individual components of the electrokymograph, certain alterations were made to permit the use of direct light stimuli. Such experiments were confined to the noncommercial models, and the commercial electrokymographs were not altered for use with direct light. The frequency response characteristics of the various components were tested as follows:

1. Frequency Response of Electrocardiographic Recorders—Four types of instruments (string galvanometer, electronic galvanometer, direct writing recorder-A, direct writing recorder-B) were tested by direct coupling with an oscillator

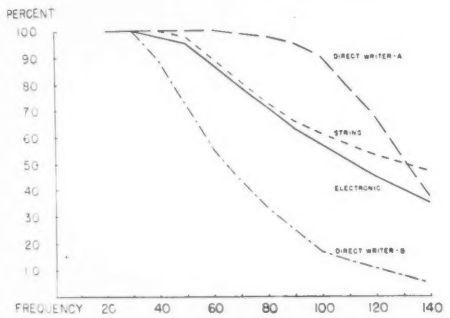

FIG. 2. Frequency response curves of various types of electrocardiographic recorders: The amplitude of response to a sine wave stimulus of standard potential difference is recorded in terms of the amplitude at 20 cycles per second.

generating a sine wave from 20 to 150 cycles per second. As shown in figure 2, with three of the instruments, the response was almost linear up to 60 cycles per second; at higher frequencies, one of these (direct writer-A) maintained amplitude to 90 cycles per second while the other two lost amplitude beyond 60 cycles per second. The fourth instrument (direct writer-B) lost amplitude rapidly at frequencies over 40 cycles per second.

2. Frequency Response of Photomultiplier Tubes—By substituting translucent paper for the strip of fluoroscopic screen, the photomultiplier tube can be subjected to a direct light stimulus in place of the x-ray. The light source is adjusted so that the phototube output is of the same order of magnitude as that resulting from stimulation of the fluorescent screen by x-ray. In this way, the conversion of light into millivolt output can be studied, while it is subjected to frequency changes caused by interposing the rotating disk described above. These effects are recorded directly by the electrocardiograph. Thus, the frequency response curves so obtained, minus the known curves for the electrocardiographic recorders as determined above, give as a difference the frequency response of the photomultiplier tube. The effects of the fluoroscopic screen and of the filter, as component parts of the electrokymograph, have

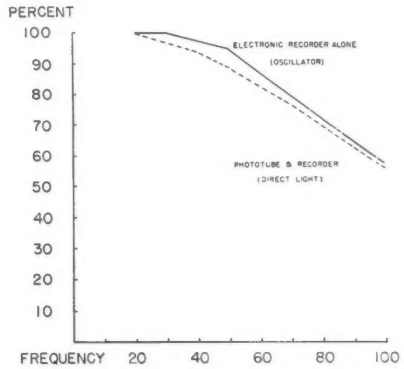

FIG. 3. Frequency response curves of electronic recorder as compared with that of the same recorder with stimulus supplied through a photo-multiplier tube: The curves are seen to be practically identical indicating that the phototube itself has little influence upon frequency response.

been eliminated. As seen in figure 3, the curves for phototube and electrocardiograph together are similar to the curves for the electrocardiograph alone, thus showing little frequency response change in the photomultiplier tube.

3. Frequency Response of Fluoroscopic Screens—The effects of the strip of fluoroscopic screen would be demonstrated by the difference between the direct light response of the phototube directly coupled into the electrocardiographic recorder, and the x-ray response of the phototube directly coupled into the same recorder. This is difficult to compare, because the x-ray response is disturbed by the cyclic interference of the x-ray beam if it is not passed through a filter. Therefore, the same filter was added to

both the direct light and to the x-ray systems. The difference will still represent the effect of the fluoroscopic screen. As seen in figure 4, this difference is very small, indicating only minor frequency response effects in the fluoroscopic screen within the frequency ranges tested.

4. Frequency Response of Filters—It is obvious from the tests of the other components, which have been shown to have relatively minimal effects on frequency response, that the filter must account for most of the total frequency response characteristics of the electrokymograph. The ideal filter would be one which cut off only the 120 cycle pulsation of the x-ray

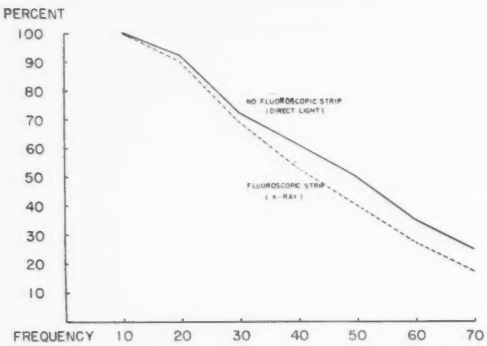

FIG. 4. Frequency response curves of electronic recorder, filter, and phototube as compared with the same system with the additional influence of the fluoroscopic strip: The latter has a small but probably significant influence upon the total frequency response.

beam, without interfering with stimuli of any other frequency. Actually, however, as a filter approaches perfection in eliminating interference at 120 cycles, it also interferes appreciably with stimuli at other frequencies. To test the effect of the filter on frequency response, it is necessary to compare the response curves resulting with and without the filter. With the x-ray as a stimulus, however, there is considerable interference when no filter is included in the circuit. Therefore, the phototube head was adapted for use with direct light as described above, and the curves compared with and without the filter, all other factors being held constant. Figure 5 shows the frequency response curve of a noncommercial filter as determined by this method. Several other noncommercial models were tested and the filters varied in the degree to which they affected the magnitude of response at different frequencies. A major reduction in frequency response was observed with each of these filters.

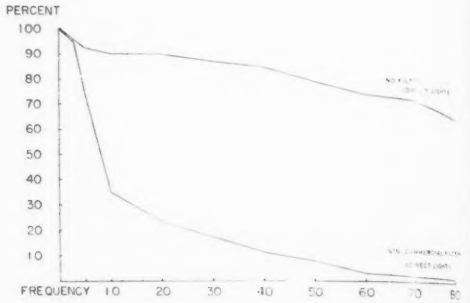

FIG. 5. Frequency response curves of the phototube and electronic recorder as compared with the same system to which a tuned 120 cycle T-type filter has been added. The enormous effect of this particular filter is evident.

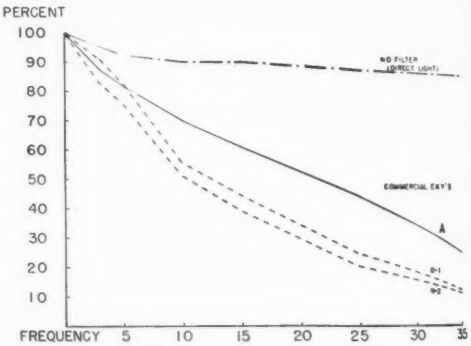

FIG. 6. Frequency response curves of the electronic recorder and phototube unit as compared with similar systems with the addition of a fluoroscopic strip and filter as employed in three commercial instruments supplied by two different manufacturers: The magnitude of amplitude loss with increasing frequencies is large but not so great as with the noncommercial filter illustrated in figure 5.

5. Frequency Response Characteristics of Commercial Models—From the above studies, it is apparent that the filter accounts for nearly all the frequency response effects of a given electrokymograph. Therefore, no attempt was made to convert the commercial models for use with direct light to study the effect of the various components. For practical purposes, it

is sufficient to test the total effect of each apparatus, and figure 6 shows these response curves for each of three commercial models. The deviation from linearity is seen to be considerably less than with instruments using noncommercial filters, but still of considerable magnitude.

6. Frequency Response of the Electrokymograph in the Recording of Cardiovascular Motions—A wave of any peculiar shape may be synthesized by adding together pure sine waves of various frequencies each at a particular amplitude.

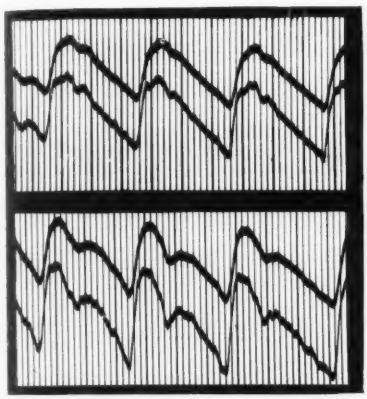

FIG. 7. Electrokymographic recordings from the aorta (top) and from the pulmonary artery (bottom): For each pair, the same phototube unit was employed. In the upper tracing of each pair, a "poor" filter was inserted between the phototube and electronic recorder, whereas in the lower tracing a standard commercial instrument was employed. A "smoothing out" of the upper, overdamped curves is apparent as well as a "time lag" in response.

Conversely a complex wave may be considered to be built up of sine waves of various frequencies and amplitudes. Thus, in order for an instrument to reproduce faithfully a voltage having a particular wave shape, it must be capable of reproducing equally well all the component sine waves present in that wave. These principles may be applied to the use of the electrokymograph in recording cardiovascular motions in the following example: The motion frequency of the major components of the dicrotic notch are at a higher frequency than those of the ejection curve. Unless the frequency response is linear, the higher frequency motions of the dicrotic notch will be recorded with relatively lesser amplitude than the lower frequency motions of the ejection wave. If this percentage reduction is great, as in an electrokymograph with a "bad" filter, the dicrotic notch may be completely lost from the wave form. Figure 7 illustrates the difference in aortic and pulmonic movements from one patient simultaneously recorded through two different electrokymographs, one of which has a "bad" filter. Note the smoothing out of the wave and the tendency to loss of the dicrotic notch as recorded through the inferior instrument. The term "overdamping" is commonly applied to this phenomenon. In the illustrations of some publications dealing with electrokymography, the wave forms have an appearance suggesting that an overdamped instrument was used.

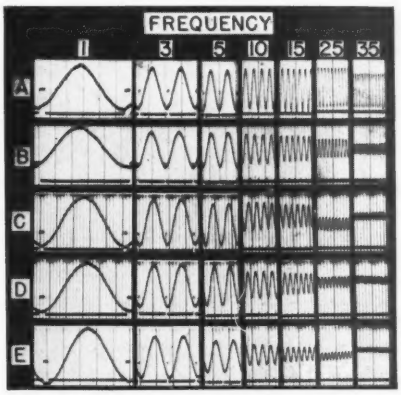

FIG. 8. The frequency response and the time lag between stimulus and response of various systems employed in electrokymography: A mechanically generated sine-wave stimulus of fixed amplitude has been recorded in unfiltered form (A) through three commercial electrokymographs (B, C and D) and through a noncommercial one (E). The frequency response effects are those which have been graphically illustrated in figure 6. At the peak of each sine wave an electrical microswitch was stimulated. It is seen that the stimulus and response coincide at all frequencies with system A. With each of the other systems the response is appreciably delayed. In the frequency range between 3 and 35 cycles per second, the delay remained fairly constant for each of the commercial instruments (B, C, and D), ranging from 0.015 to 0.025 second. For the noncommercial system (E), the lag at low frequencies was greater and at higher frequencies was about the same as with the commercial recorders.

Fidelity of the Electrokymograph in Recording Time

During certain experiments designed to test the frequency response characteristics of the electrokymograph, a standard sine wave was recorded both by direct couple and after passage through a filter. The resultant waves recorded simultaneously did not superimpose, but rather the filtered wave definitely lagged in reference to the unfiltered wave.

To study this phenomenon, a switch was mounted on the eccentric cam in a manner such that a closed circuit would mark either the exact peak or valley of the sine wave. Thus the lag between this signal and actual recording of the corresponding point of the wave could be measured. In this manner, the time lag of various electrokymographs was determined at different frequencies. This time lag should vary with different electrokymographs, and also with the same electrokymograph at various frequencies, depending chiefly on the characteristics of the filter.* The time lag in the phototube and in the electrocardiograph should be negligible. Thus, sine waves recorded by direct light with no filter show no measurable lag (see figure 8A). Figure 8 shows the time lag of three commercial electrokymographs (8B, C and D) and one noncommercial model (8E) at various frequencies up to 35 cycles per second. The loss of amplitude with increase of frequency is also illustrated.

Discussion

The electrokymograph has been employed to record border movements and changes in roentgen opacity of the heart and great vessels. Ideally, the recorded movements should be simultaneous with and directly proportional in magnitude to the dynamic events being investigated. Actually, the commercial instruments tested deviated from these ideals in three important respects:

1. The sensitivity of the various portions of the reception slot of the phototube was not uniform. Toward each end of the slot the sensitivity was reduced drastically. The most sensitive portion was near the center, but in this zone, only 9 mm. was available if an amplitude error of not greater than 15 per cent was tolerable. The center of this zone of relative linearity was displaced about 2 mm. toward the base of the tube from the geometric center of the slot, indicated on the instrument by the centering knobs. Thus, it is theoretically possible to record a movement of not greater than 8 mm., with an amplitude error of not greater than 15 per cent, provided that centering of the image is maintained within 1 mm. of the center of the maximum sensitivity zone. With most careful technic it is difficult to maintain centering within a zone of less than 4 mm. (the knobs are 3 mm. wide), and it is customary to center at the diastolic position of the border rather than at the midpoint of the range of excursion of the border. Thus, although most border movements to be recorded are of 4 mm. amplitude or less, the entire excursion of the border movement is kept within the linear zone only with most careful attention to technic. If the centering knobs are employed, any excursion of more than 2 mm. beyond the edge of the knob toward the free end of the tube will be recorded with appreciably reduced amplitude. The significance of these observations as they pertain to interpretation of wave amplitudes and wave shapes is apparent.

2. A time interval elapsed between the instant at which a movement occurred and the instant at which it was recorded. The amount of this time lag in a given instrument depended upon the rapidity of the movements. For the commercial instruments, this time lag ranged from .015 to .025 second within the frequency range tested. For many of the purposes to which the electrokymograph has been applied, this limitation of the instrument has no bearing upon the interpretation of the results. Obviously it has little influence on the interpretation of gross alterations of wave form as, for example, in paradoxical movement of infarcted myocardium. Likewise, there is no error in determining time differences between two dynamic events electrokymographically recorded, when each is compared with a third event (e.g. in

* For the type of circuit employed in these filters the time delay decreases with increasing frequencies, falling to zero at the frequency to which the filter is tuned.

determining bundle branch block by delay of electrokymographic pulsations of either the pulmonary artery or aorta as compared with the carotid pulse[8]). However, where the instrument is to be employed in the direct time correlation of dynamic events with murmurs, sounds, or electrical activity, the time lag may be of considerable importance. If the time lag of the particular instrument employed has been established, an approximate correction can be made, since within the range of frequencies with which one is concerned, the time lag is reasonably constant.

3. The recorded amplitude of a movement of standard magnitude diminished with increasing rapidity of the movement. The influence of this frequency response characteristic of each instrument as applied to complex wave forms is difficult to assess quantitatively. The degree of frequency change resulting from simple variations in pulse rate is probably too small to have any appreciable bearing. Conversely, an important distortion in the finer details of wave shape, especially of rapid movements such as those manifested in the dicrotic notch, must occur. This probably accounts, at least in part, for the "smoothed out" appearance of recordings from the aorta and pulmonary artery. In many records, especially from the aorta, the dicrotic notch is either absent or indicated merely by a deviation of the downstroke from the peak of the ejection wave.

In these studies a quantitative analysis of the recording fidelity of three commercial instruments has been made. The linearity characteristics of the phototube receptor slot will probably be found to be essentially similar in all instruments. The time lag and frequency response characteristics vary from instrument to instrument. These are almost entirely contingent upon the characteristics of the filters employed in damping out the cyclic pulsations of the x-ray beam. We have studied only those instruments adapted for use with a 120 cycle, full-wave rectified fluoroscope. Instruments are also in use with 60 cycle, half-wave rectified x-ray equipment. Since a filter tuned to 120 cycles is characteristically sharper than one tuned to 60 cycles, the time lag and frequency response characteristics of the latter instruments are likely to be appreciably farther from the ideal of recording fidelity than the instruments which we have tested.

It is apparent from these studies that for many of the problems to which the electrokymograph has been and will be applied, an exact measure of the recording characteristics of the specific instrument employed is essential to the accurate interpretation of the results.

Summary

1. Studies were made of the recording fidelity of several electrokymographs including three commercial models. Investigation was directed toward the quantitative estimation of defects in linearity, frequency response, and time lag. From these studies it was possible to differentiate the contribution of each component part of the electrokymograph to the defects observed.

2. From the ideal of instantaneous recording, directly proportional in magnitude to the dynamic event under study, deviations were of three types: (a) The sensitivity of the receptor slot of the phototube was not uniform. (b) A time lag, varying in these instruments from .015 to .025 second, between the event and the recording of the event, was observed. This was almost entirely a function of the filter. (c) The recorded amplitude of a movement of standard magnitude diminished with increasing rapidity of the movement. This was also a function of the filter.

3. The significance of these deviations from ideal recording fidelity, as applied to the clinical use of the electrokymograph in the study of cardiovascular dynamics, is discussed.

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The Interrelationships of Serum Cholesterol, Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease

By MENARD M. GERTLER, M. D., M. Sc., STANLEY MARION GARN, Ph. D., AND JACOB LERMAN, M. D.

Serum cholesterol (free, esters and total) and serum phospholipids were determined in 97 men who had experienced coronary heart disease prior to the age of 40, 146 healthy nonhospitalized men of comparable age and a group of 97 men who were "matched" to the coronary disease group. The mean values for serum cholesterol (total) were 286 mg. per 100 cc., 224 mg. per 100 cc., and 247 mg. per 100 cc. for the coronary disease group, control group and matched control group, respectively. The serum phospholipids were highest in the coronary disease group. It is demonstrated that the interrelationships of the lipids in coronary heart disease are more important than any one of the constituents taken by itself. The theoretic implications of the total cholesterol: phospholipids ratio are considered.

THE STEROL group, of which cholesterol is a member, is a term restricted to those crystalline alcohols found in unsaponifiable fractions of oils and fats, but not wax.[1] The structure has been tentatively accepted as a phenanthrene-cyclopentane or "cholane" form of sterol ring.[2] Possibly the earliest association between cholesterol and atherosclerosis was Vogel's observation[3] in 1841 that cholesterol was present in atherosclerotic lesions. Windaus[4] analyzed various diseased aortas in 1910 and reported that there was six times as much cholesterol and twenty times as much esterified cholesterol in the atherosclerotic aorta as that observed in the normal aorta. Schoenheimer[5] and others[6, 7] extended these observations and concluded, after chemical analyses of many aortas, that the proportion of lipids in the aortas increased with age and atherosclerosis.

As a result of these observations, investigators, both clinical and experimental, began to study the interrelationship of the level of serum cholesterol and the degree of atherosclerosis. Experimentalists, led by Anitschkow and Chalatow,[8] produced atherosclerosis in the rabbits by feeding the animals large quantities of cholesterol. Clinicians attempted to learn whether the incidence of atherosclerosis in the clinical and "normal" population without hypercholesterolemia was higher than in individuals in whom hypercholesterolemia existed. Thus, individuals with hereditary hypercholesterolemia,[9] nephrosis,[10] hypothyroidism,[11] xanthomatosis,[12] diabetes mellitus[13, 14] are purported to show higher incidence of atherosclerosis.

Duff[15] questions the validity of assuming that Anitschkow's experiments apply to man. Duff reasons that the rabbit is an herbivorous animal and, under normal circumstances, does not ingest animal cholesterol. Thus, when inordinately high amounts of animal cholesterol are fed to rabbits, there is no available mechanism to handle this foreign substance, and atherosclerotic lesions develop. Duff noted that the atherosclerotic plaques in the experimental rabbits differed from those in man in their distribution.

Leary,[16] on the other hand, after repeating Anitschkow's animal experiments and after examining the coronary arteries of thousands of cases of coronary heart disease, arrived at the same conclusions as Anitschkow, and, of course, he suggests a direct causal relationship between serum hypercholesterolemia and atherosclerosis.

There is no satisfactory evidence which entirely confirms or denies that there is a causal

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relationship between the state of hypercholesterolemia and atherosclerosis. Landé and Sperry[17] and others[18, 19] maintain from their clinical analysis of autopsy material that no relationship exists between hypercholesterolemia and atherosclerosis. The association between hypercholesterolemia and cardiovascular diseases is denied by several investigators.[20, 21] However, the bulk of the evidence is in favor of this association.[22–27] We must consider that the evidence for the existence of a higher incidence of atherosclerosis in individuals who have diseases which manifest a hypercholesterolemia cannot be accepted as conclusive evidence of a causal relationship; there is the possibility that both atherosclerosis and hypercholesterolemia are the two end products of an altered metabolic state. This possibility is further strengthened by Lerman and White's[25] observations that in individuals who had experienced myocardial infarction prior to the age of 40, the serum cholesterol was higher and the basal metabolic rates were lower than in suitable controls. Steiner and Kendall[28] extended this finding and experimentally produced atherosclerosis in dogs by feeding them thiouracil during maintenance of a high cholesterol diet. They thus confirmed Shapiro's[29] observations that thyroidectomy and other alterations of the glandular state favored the development of atherosclerosis. Thus, it is reasonable to suggest that atherosclerosis may be the end result of the combination of both an altered biochemical and an altered hormonal metabolism and that hypercholesterolemia may be one sign of this abnormality.

There is some evidence that serum cholesterol and cholesterol esters may not be the most important lipids in coronary artery disease. Serum phospholipids and, particularly, the ratio between serum cholesterol and serum phospholipids are altered in several diseases to as important a degree as either of the two lipids considered separately.[30, 31] This question has been considered in this paper.

Simultaneously with the progress of this work, it has been shown that rabbits receiving Tween 80 and cholesterol did not develop atherosclerosis in spite of an elevated serum cholesterol.[32] Concomitant with the rise in serum cholesterol there was an increase in serum phospholipids which the authors claim tended to prevent the development of atherosclerosis. Hueper[33] stresses the importance of lecithin as a colloidal stabilizer, and other authors have extolled its efficacy in prevention of atherosclerosis in man[34] and experimental animals.[35] The question of the cholesterol:phospholipids ratio in coronary artery disease has been under consideration in this laboratory, and the findings and interpretations of the results will be included in this paper.

The paper will also consider the serum values of cholesterol (total, free and esters), phospholipids and the various interrelationships among these variables in health and in coronary artery disease. The role of cholesterol in the development of atherosclerosis will be discussed. Furthermore, the range of normal serum cholesterol values will be considered, and the influence of body build and age will be discussed.

Method

This study was conducted on three groups of men: a coronary disease group of 97 individuals, a healthy control group of 146 individuals, and a matched control group of 97 individuals. The coronary disease group consisted of individuals who had experienced a myocardial infarction prior to the age of 40 years. The control group consisted of executives, office personnel and plant workers, comparable in age to the coronary disease group, who were healthy at the time of examination. The matched control group consisted of individuals, each of whom matched one member of the coronary disease group in age, body build, weight, ancestry, and occupation. This group was included in order to determine to what extent these variables, rather than coronary heart disease itself, affected the serum lipids.

The blood samples were drawn at any time during the day, not only because of expediency, but also because fasting specimens offer no particular advantage insofar as accuracy is concerned.[36, 37] The Bloor methods[38, 39] for determining total cholesterol and cholesterol esters were employed throughout this study. In this laboratory, Miss Margaret Rourke has found that they give as accurate, dependable and comparable results as the Schoenheimer-Sperry technic.[40] Serum phospholipids were determined by the Fiske and Subbarrow technic.[41]

Results

The results of the chemical determinations of the serum levels of total cholesterol, chol-

esterol esters, free cholesterol and phospholipids are tabulated in class intervals of 30 mg. per cent. The distribution of the array by class intervals, the range, the mean, and the standard error of the mean are given for each distribution. The tables include the data from three groups of individuals: (a) control group, (b) coronary disease group, and (c) matched control group.

A. *Serum Cholesterol (Total, Esterified and Free) and Serum Phospholipids (Tables 1–4).*

The mean total serum cholesterol in the control group (224.4 ± 3.5 mg. per cent) compares favorably with other published values.[42–45]

TABLE 1.—*Total Serum Cholesterol in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

Serum Cholesterol	Control Group	Coronary Disease Group	Matched Control Group
120–149	2	0	0
150–179	23	2	9
180–209	33	9	18
210–239	37	15	28
240–269	27	13	14
270–299	17	18	17
300–329	6	22	6
330–359	2	7	3
360–389	0	5	0
390–419	0	3	1
420–449	0	0	0
450–479	0	0	1
480–509	0	3	0
Number	146	97	97
Range	148–332	167–490	155–455
Mean ± s.e.	224.4 ± 3.5	286.5 ± 6.6	241.9 ± 5.5

If distribution curves are plotted for the control group, matched control group, and the coronary disease group, one immediately notices a considerable area of overlap. It was calculated from the data that 8.2 per cent and 15.4 per cent of the control group and matched control group, respectively, exceed the mean value of total serum cholesterol (286.3 mg. per cent) of the coronary group. No one in the control group and only two individuals in the matched control group possessed serum cholesterols greater than 352.0 mg. per cent (which is the value of the mean plus one standard deviation of the coronary disease group). Twenty-four members of the coronary disease group (23 men and 1 woman) possessed a serum cholesterol below the mean serum cholesterol of the normal group. Two patients with coronary artery disease (1 man and 1 woman) possessed a serum cholesterol below 181.0 mg. per cent, which is the mean value minus one standard deviation of the control group. The mean value of serum cholesterol of the coronary disease group is significantly higher than the mean value of serum cholesterol in either the control group or the matched control group.

The results for cholesterol esters compare favorably, although somewhat on the low side, with the values obtained from the literature.[47]

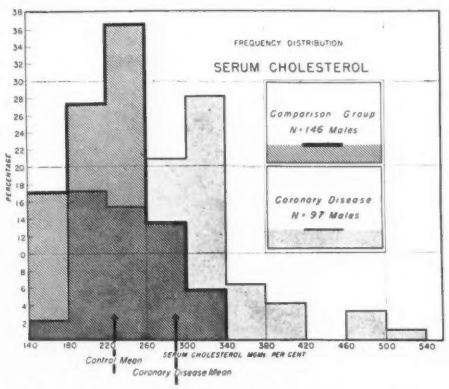

FIG. 1. Serum Cholesterol in the Control Group and the Coronary Heart Disease Group.

As in the total serum cholesterol, there is a considerable overlap of the range of values for all three groups—6.8 per cent and 19.6 per cent of the control group and the matched control group, respectively, exceed the mean value of serum cholesterol esters (176.7 mg. per cent) of the coronary disease group. Again, no one in the control group and only two individuals in the matched control group exceed the value of the mean plus one standard deviation (230.0 mg. per cent) of the coronary disease group. The value of serum cholesterol esters in sixteen members of the coronary disease group was below the control mean (124.6 mg. per cent), and in only three individuals of the coronary disease group did the value of serum cholesterol esters fall below the mean minus one standard

deviation (93 mg. per cent) of the control group. The mean value of serum cholestrol esters of the coronary disease group is markedly greater than the mean value of serum cholesterol esters in either the control group or the matched control group.

The results for free cholesterol are somewhat higher than is generally encountered in the literature.[27, 47] However, since all three groups were studied in the same manner, the results are comparable.

Again, there is a considerable overlap in the level of free cholesterol in the serum. There are

TABLE 2.—*Serum Cholesterol Esters in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

	Control Group	Coronary Disease Group	Matched Control Group
50–79	4	0	1
80–109	49	6	23
110–139	50	19	25
140–169	32	22	27
170–199	8	20	13
200–229	3	16	5
230–259	0	6	1
260–289	0	3	1
290–319	0	0	0
320–349	0	0	0
350–379	0	2	0
Number	146	94	97
Range	72–223	88–376	70–260
Mean ± s.e.	124.6 ± 2.6	176.7 ± 5.5	141.0 ± 3.9

53 individuals (36 per cent) and 37 individuals (38.1 per cent) in the control group and the matched control group, respectively, whose free cholesterol exceeds the mean value of free cholesterol (110.4 mg. per cent) in the coronary disease group. There are 8 individuals (5.5 per cent) in the control group and 6 individuals (5 per cent) in the matched control group, whose free cholesterol exceeds 148 mg. per cent (mean value plus one standard deviation of the coronary disease group). Thirty-seven individuals in the coronary disease group possess serum free cholesterol levels below 99.7 mg. per cent (mean value of the control group), while ten individuals in the coronary disease group possess serum free cholesterol values below 71.4 mg. per cent (mean value minus one standard deviation of the control group). The mean value of serum free cholesterol in the coronary disease group is significantly higher than the mean value of serum free cholesterol in either the control group or the matched control group.

TABLE 3.—*Free Cholesterol in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

	Control Group	Coronary Disease Group	Matched Control Group
30–49	5	5	3
50–69	15	4	10
70–89	34	17	26
90–109	39	22	21
110–129	31	24	22
130–149	15	8	9
150–169	6	7	4
170–189	1	4	1
190–209	0	1	0
210–229	0	2	1
Number	146	94	97
Range	33–174	37–227	45–216
Mean ± s.e.	99.7 ± 2.3	110.4 ± 3.9	100.8 ± 3.9

TABLE 4.—*Serum Phospholipids* in the Control Group, the Coronary Disease Group and the Matched Control Group.*

	Control Group	Coronary Disease Group	Matched Control Group
180–209	0	1	0
210–239	10	5	4
240–269	22	5	12
270–299	47	12	28
300–329	33	11	20
330–359	22	17	15
360–389	10	6	10
390–419	2	4	1
Number	146	61	90
Range	213–415	195–414	221–397
Mean ± s.e.	299.3 ± 3.3	316.4 ± 6.7	305.7 ± 4.2

* Serum phospholipids are expressed as lecithin which is here considered to be 25 times the serum lipid phosphorus level.

The maximum difference between the coronary disease group and the two control groups is found in the cholesterol esters, and very little difference exists in the free cholesterol. Hence, the higher total cholesterol is largely due to the esterified fraction.

The mean of the serum phospholipids exceeds the means reported in the literature.[31, 44] Again, there is considerable overlap of the three distribution curves, with the coronary artery disease group showing the highest mean.

TABLE 5.—*Cholesterol Esters: Total Cholesterol Ratio in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

Per Cent	Control Group	Coronary Disease Group	Matched Control Group
35.0–39.9	2	2	1
40.0–44.9	15	6	5
45.0–49.9	28	3	12
50.0–54.9	33	12	18
55.0–59.9	22	18	15
60.0–64.9	19	18	19
65.0–69.9	15	14	13
70.0–74.9	10	12	11
75.0–79.9	1	7	3
80.0–84.9	1	2	0
Number	146	94	97
Range	38.7–83.4	36.0–84.2	39–79
Mean ± s.e.	55.61 ± .77	61.43 ± 1.06	58.5 ± .90

TABLE 6.—*Free Cholesterol: Total Cholesterol Ratio in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

Per Cent	Control Group	Coronary Disease Group	Matched Control Group
15.0–19.9	1	2	0
20.0–24.9	1	7	2
25.0–29.9	10	12	10
30.0–34.9	15	14	9
35.0–39.9	18	18	21
40.0–44.9	23	18	15
45.0–49.9	32	12	17
50.0–54.9	29	3	14
55.0–59.9	15	6	6
60.0–64.9	2	2	3
Number	146	94	97
Range	16.6–61.3	15.8–64.0	21–61
Mean ± s.e.	44.39 ± .76	38.57 ± 1.06	41.9 ± .97

Although the mean value of serum phospholipids in the coronary disease group exceeds the mean values of serum phospholipids in the other two groups, the difference is significant only in comparison to the control group.

B. *Ratios* (*Tables 5–12*).

The relationship of the various forms of cholesterol (free, esterified and total) to each other has been stressed in hepatic disorders[48] and certain forms of epilepsy,[49] and mentioned in cardiovascular diseases.[27] The ratio, total cholesterol: phospholipids, has not been stressed in human coronary heart disease or atherosclerosis. The ratios which are to be considered here are (a) cholesterol esters: total cholesterol; (b) free cholesterol: total cholesterol; (c) free

TABLE 7.—*Free Cholesterol: Cholesterol Esters Ratio in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

Per Cent	Control Group	Coronary Disease Group	Matched Control Group
10.0–29.9	2	4	2
30.0–49.9	20	24	19
50.0–69.9	30	28	28
70.0–89.9	32	24	16
90.0–109.9	31	5	16
110.0–129.9	19	2	11
130.0–149.9	10	5	3
150.0–169.9	2	0	2
170.0–189.9	0	2	0
Number	146	94	97
Range	19.9–158.2	18.8–178.0	26.3–158.2
Mean ± s.e.	84.76 ± 2.47	68.19 ± 3.09	76.96 ± 2.99

TABLE 8.—*Total Cholesterol: Phospholipids Ratio in the Control Group, the Coronary Disease Group, and the Matched Control Group.*

Per Cent	Control Group	Coronary Disease Group	Matched Control Group
48.0–55.6	3	0	1
56.0–63.6	24	3	14
64.0–71.6	34	2	18
72.0–79.6	36	14	16
80.0–87.6	32	9	26
88.0–95.6	11	8	7
96.0–103.6	5	13	6
104.0–111.6	1	9	1
112.0–119.6	0	0	1
120.0–127.6	0	0	0
128.0–135.6	0	2	0
Number	146	60	90
Range	52.0–105.6	57.80–132.04	51.84–114.6
Mean ± s.e.	74.08 ± .9	89.48 ± 2.4	77.60 ± 1.32

cholesterol:cholesterol esters; (d) total cholesterol:phospholipids.

In tables 5 to 8 are listed the sample size, range, mean and standard error of the four ratios (1) cholesterol esters:total cholesterol; (2) free cholesterol:total cholesterol; (3) free cholesterol:cholesterol esters; (4) total cholesterol:serum phospholipids. The means and their standard errors of the four lipids considered and the four ratios are summarized in table 9. In all four lipids and all four ratios the coronary group differs from the two control groups. All differences are significant except for difference in phospholipids between the coronary and the matched control group (see table 10).

TABLE 9.—*Summary of the Means and Their Standard Errors of the Four Lipids and Four Indicial Ratios of the Control Group, the Coronary Disease Group, and the Matched Control Group*

	Control Group	Coronary Disease Group	Matched Control Group
Free Cholesterol	99.69 ± 2.33	110.36 ± 3.86	100.8 ± 3.50
Cholesterol esters	124.63 ± 2.6	176.66 ± 5.47	141.0 ± 3.88
Total cholesterol	224.42 ± 3.53	286.51 ± 6.59	241.9 ± 5.50
Phospholipids	299.32 ± 3.33	316.42 ± 6.7	305.7 ± 4.17
Cholesterol esters / Total cholesterol	55.61 ± 0.77	61.43 ± 1.06	58.5 ± 0.90
Free cholesterol / Total cholesterol	44.39 ± .76	38.57 ± 1.06	41.9 ± .97
Free cholesterol / Cholesterol esters	84.76 ± 2.47	68.19 ± 3.09	76.96 ± 2.99
Total cholesterol / Phospholipids	74.1 ± .92	89.4 ± 2.04	77.6 ± 1.32

TABLE 10.—*Degree of Significance between the Three Groups with Respect to the Lipids and Indices Listed in Table 9.*

	Control and Coronary Groups	Coronary and Matched Groups	Control and Matched Groups
Free cholesterol	*	*	n.s.
Cholesterol esters	**	**	**
Total cholesterol	**	**	*
Phospholipids	*	n.s.	n.s.
Cholesterol esters / Total cholesterol	**	*	*
Free cholesterol / Total cholesterol	**	*	n.s.
Free cholesterol / Cholesterol esters	**	*	*
Total cholesterol / Phospholipids	**	*	n.s.

n.s., not significant; *, significant; **, highly significant.

TABLE 11.—*Coefficients of Variation of the Four Lipids in the Three Groups*

Lipid	Control Group	Coronary Disease Group	Matched Control Group
Free cholesterol	28.29	33.92	38.1
Cholesterol esters	25.19	30.00	27.1
Total cholesterol	18.98	22.64	22.2
Phospholipids	13.44	16.48	12.93

TABLE 12.—*Coefficient of Correlation between Total Cholesterol and Other Variables in the Control Group and the Coronary Disease Group.*

Variable	Control Group Coronary	Disease Group
Fat intake	−.07 ± .08 n.s.	−.10 ± .10 n.s.
Protein	−.02 ± .08 n.s.	−.10 ± .09 n.s.
Phospholipids	+.66 ± .05 **	+.51 ± .09 **
Uric acid	+.10 ± .08 n.s.	+.01 ± .10 n.s.

n.s., not significant; *, significant; **, highly significant.

The degree of variability of the four lipids may be assessed by either comparing the coefficient of variation or the standard deviations.[50] The coefficients of variation express variation as a percentage of the mean. Table 11 indicates that the coronary disease group is more variable in all four lipids considered than

either the control group or the matched control group.

In order to determine the strength of the relationship between total cholesterol and other variables, the coefficient of correlation was calculated between cholesterol and other variables.[50] The results for these calculations are discussed in several of the papers which follow, but the correlations with the variables which are not discussed are considered here in table 12. It is seen from table 12 that serum cholesterol is highly correlated with serum phospholipids in both the control group and the coronary disease group. As serum cholesterol increases, the serum phospholipids increase as well.

Discussion

The observations in this paper confirm the present day views that the total cholesterol in the serum is elevated in patients who have experienced myocardial infarction.[25] Changes in the other lipids such as free cholesterol, cholesterol esters and phospholipids have been demonstrated in other diseases from time to time, but the possible relationship with coronary artery disease requires further clarification.

A matched control group is included, composed of individuals who are not only healthy, but in which each resembles an individual with coronary heart disease in height, weight, age, body build, ethnic origin and occupation. This group offers a better comparison series than the usual random sample of healthy males. The difference in the serum lipids of the three groups is as expected. The four blood lipids in the coronary disease group exceed those of the other two groups. This is in keeping with the known facts on the subject. The difference, however, between the ordinary control group and the matched control group is statistically significant—a very interesting finding in two healthy groups.

As is shown in our second paper, the coronary disease group is predominantly mesomorphic at the expense of the endomorphic and ectomorphic physiques.[51] It is also demonstrated that the serum lipids are higher, normally, by at least 30 mg. per cent in the endomorphic and mesomorphic groups than in the ectomorphic group.[52] The matched control group differs as much from the control group in body build as does the coronary disease group. Accordingly, one would expect to find in the matched control group a higher degree of mesomorphy at the expense of ectomorphy, and hence a greater value for serum lipids than the normal. Another contributing factor to the difference in serum lipids between the control group and the matched control group is the fixed relationship between mesomorphy and coronary artery disease; and as the number of mesomorphs increase, the number of potential coronary patients increases, and consequently serum cholesterol could be expected, on a chance basis, to increase as well.

A causal relationship between atherosclerosis and cholesterol has been concluded from the observation that serum cholesterol is elevated in individuals who experience cardiovascular diseases. There is no evidence from the present results which would suggest a threshold level for the development of atherosclerotic coronary disease, although the existence of individual thresholds may be possible.

The mechanism by which cholesterol and cholesterol esters enter the intima is not known. The source of the cholesterol in the serum is thought to be derived mainly from endogenous sources and to some degree from exogenous sources. It is not known whether the cholesterol in the atherosclerotic plaque is derived from the exogenous or endogenous sources. Leary[16] favors the exogenous source and further suggests that the Kupffer cells remove the excess cholesterol esters from the liver, transport them through the lungs and thence to the subendothelial layers of arterial intima at the most accessible region. Leary finds support for his theory by leaning on Gordon's[53] observations that the most probable points of atherosclerosis are in the arterial regions where pulsatile intermissions are the most prominent.

Moreton has contended that the postprandial episodes of hyperchylomicronemia following the intake of fatty meals may be responsible for atherosclerosis.[54] Pollak[55] has confirmed Moreton's tenets by demonstrating the deposition of cholesterol in the rabbit's arterial intima a few minutes after its injection intravenously. The recent work by Ladd and his co-workers[32]

on rabbits confirms, experimentally, observations which this project has made for several years on individuals with coronary artery disease. These authors believe that the total cholesterol:phospholipids ratio is important in preventing a deposition of cholesterol in the arterial endothelium. From their experiments, they concluded that the total cholesterol:phospholipids ratio is an important factor in experimental atherosclerosis, and that increased blood phospholipids may modify or prevent the development of atherosclerosis.

The serum phospholipids and serum cholesterol are statistically higher in the coronary disease group than in the control group, but by different degrees. The cholesterol:phospholipids ratio is also significantly increased in the coronary disease group in contrast to the normal group. This ratio is also increased in hypothyroidism,[30] and, on analysis, the reasons for the increase are obviously different. In coronary heart disease the rise in serum cholesterol is greater than the corresponding rise in serum phospholipids, while in hypothyroidism the serum cholesterol rises considerably in the absence of any change in serum phospholipids.

Coefficients of correlation and partial coefficients of correlation were calculated in an effort to obtain more insight into the serum interrelationships.[50] In the normal group, the correlations between age and serum cholesterol, and age and serum phospholipids are $+0.30 \pm .08$ and $+0.43 \pm .07$. These correlations are not significantly different. The correlations calculated for the coronary disease group between age and serum cholesterol, and age and serum phospholipids are $+.16 \pm .10$ and $+.20 \pm .12$ respectively. These approach, but do not reach, significance. This suggests that the lipid relationships were disturbed in the coronary disease group. Additional suggestions were obtained from the partial correlations. The partial correlations between cholesterol and phospholipids with age held constant are $+.62 \pm .05$ and $+.50 \pm .10$ for the control group and the coronary group respectively. The partial correlations between age and cholesterol with serum phospholipids held constant are $+.05 \pm .08$ and $+.07 \pm .10$. (These partial correlations are not significantly different from zero.) The partial correlations between age and phospholipids with serum cholesterol held constant are $+.32 \pm .07$ and $+.14 \pm .13$ for the control group and the coronary disease group respectively. (The latter correlation is not significant.) Thus, it is observed that the serum phospholipids continue to show an age correlation in the normal group, but the trend is insignificant in the coronary disease group. Serum cholesterol, on the other hand, failed to show age changes in either group with the serum phospholipids held constant. Thus, the normal age increments are absent in the coronary disease group, while serum phospholipids appear to mediate the normal cholesterol–age relationship in some way in the normal group. It is therefore reasonable to suggest that the phospholipids play a role in the normal age change in serum cholesterol. The failure to find such a serum cholesterol change in coronary artery diseae may merely reflect the basic difference in amount and proportion of the serum phospholipids in this disease group.

Summary

1. The serum cholesterol, serum cholesterol esters, free cholesterol and phospholipids were determined in three groups of individuals: a coronary disease group of 97 males, a control group of 146 males, and a matched control group of 97 males. The ratios of the various lipids were also determined for each individual in each of the three groups.

2. The coronary heart disease group markedly exceeded the two control groups in values of serum cholesterol (total, free and esterified) and in serum phospholipids. However, the maximal difference was in the serum cholesterol esters, while the minimal difference was in the free cholesterol. Thus, the higher total serum cholesterol in coronary heart disease reflects the altered level of the esterified fraction.

3. The ratio, total cholesterol:phospholipids, also showed a marked difference between the coronary disease group and the two control groups, the mean ratio being 89 ± 2, $74 \pm .9$ and 78 ± 1.3 respectively.

4. The difference in total cholesterol:phospholipids ratio between the coronary disease group and the two healthy groups indicates a

disturbance in the lipid interrelationships in coronary heart disease. This is suggestive of a disturbance in serum colloidal makeup in the coronary disease group.

5. The theoretic benefits of reestablishing the increased serum cholesterol: phospholipids ratio in coronary heart disease to values characteristic of a normal population have been considered.

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The Effects of Intravenous Aminophylline upon the Coronary Blood-Oxygen Exchange

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The effects of intravenous injections of aminophylline on the coronary blood flow, cardiac oxygen consumption, cardiac work, and cardiac rate were studied by catheterization of the right ventricle and coronary sinus in anesthetized dogs. There was no substantial increase in coronary flow when cardiac activity increased following injection of the drug; this suggested that the oxygenation of the myocardium in general was not improved. Further studies on coronary blood-oxygen saturations substantiated this concept as pertaining to the infarcted heart of dogs as well as the normal. Nitroglycerin however increased general myocardial oxygenation in normal hearts.

IN AN earlier publication from this laboratory[5] it was pointed out that an estimation of the probable therapeutic value of a coronary vasodilator drug requires more information than simple measurements of coronary blood flow and arterial pressure. More specifically, a considerable (average 45 per cent) increase in coronary blood flow following large doses of nikethamide in dogs proved, upon analysis by methods now available for the purpose, to be due mainly to a decrease in mechanical efficiency of the myocardium, for which the coronary vasodilation provided only partial and imperfect compensation. It was concluded that the drug had a deleterious effect upon the heart even though it increased coronary flow and cardiac output while leaving the cardiac rate almost unchanged and lowering the mean blood pressure. The present paper reports the results of a similar study with aminophylline which is used even more widely than nikethamide for the purpose of increasing coronary blood flow.

I. Effect of Aminophylline on Coronary Blood Flow, Cardiac Energetics and Metabolic Changes

Methods. Under pentobarbital sodium anesthesia (30 mg./Kg.), the coronary flow of nine normal intact dogs was studied by the nitrous oxide method of Kety and Schmidt[15] through catheterization of the coronary sinus by the technic of Goodale and associates.[14] Other procedures necessary to estimate cardiac output by the direct Fick method and cardiac work were employed as described previously by Eckenhoff and co-workers.[6]

An experimental procedure consisted of a control period and a period of reaction to an intravenous injection of Aminophylline, U.S.P. Each period began with a measurement of cardiac output of 5 to 7 minutes duration followed by the usual 10 minute estimation of coronary flow. An interval of approximately thirty minutes was necessary between the control period and the period of reaction to drug injection to allow the animal to eliminate the nitrous oxide previously respired.[16] Following this thirty minute interval, Solution Aminophylline U.S.P. in a dosage of 4 mg. per kilogram was injected into a saphenous vein over a one minute period. As soon as the blood pressure stabilized (one to three minutes), the second set of measurements was made; four complete experiments were performed. Five control experiments were similarly performed except that no drug was injected.

Results. The data in table 1 include all measurements of the completed drug action experiments. Table 2 summarizes the mean values of important cardiac functions and the mean changes in control experiments as well as the completed drug action experiments.

The most significant changes produced by aminophylline (table 2) are the increases in cardiac output and cardiac work along with a decrease in peripheral resistance. With no significant compensatory increase in coronary blood flow, an increased cardiac oxygen consumption was observed; there was a tendency toward a drop in coronary venous oxygen con-

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TABLE 1.—*Cardiac and Respiratory Changes with Intravenous Aminophylline*

Experiment	9		10		16		24	
Dog Weight	28.0 K.		17.7 K.		16.8 K.		28.2 K.	
	Before	After	Before	After	Before	After	Before	After
Coronary Flow (cc./100 Gm. heart/min.)	109	135	103	98	73	79	135	113
Cardiac O_2 Consumption (cc./100 Gm. heart/min.)	9.7	13.7	10.2	11.7	9.2	9.9	17.5	15.4
Arterial O_2 Content (vols. %)	10.9	11.8	13.8	14.1	15.9	15.1	15.4	16.1
Mixed Venous O_2 Content	7.4	8.8	10.4	11.4	12.2	11.5	10.5	10.8
Coronary Ven. O_2 Content	2.0	1.7	3.9	2.1	3.4	2.5	2.4	2.4
Arterial CO_2 Content (vols. %)	41.7	40.2	44.1	32.4	35.2	33.2	48.3	44.1
Mixed Venous CO_2 Content	44.4	42.5	46.2	35.4	37.5	37.4	51.3	47.6
Coronary Venous CO_2 Content	49.4	47.8	52.8	45.3	47.0	45.0	56.5	53.0
Coronary A-V Difference O_2 Content (vols %)	8.9	10.1	9.9	12.0	12.5	12.6	13.0	13.7
Coronary A-V Difference CO_2 Content	7.7	7.6	8.7	10.9	11.8	12.0	8.2	8.9
R. Q. of Heart	.87	.75	.88	.91	.95	.95	.63	.65
O_2 Utilization by Heart (%)	81.5	84.8	71.7	85.2	78.7	83.5	84.5	85.2
Systemic A-V Difference O_2 (vols. %)	3.6	3.0	3.4	2.7	3.7	4.0	4.9	5.3
Systemic A-V Difference CO_2	2.7	2.3	2.1	3.0	2.3	4.2	3.0	3.5
True Inspired O_2 (cc. O_2/min.)	132	151	105	117	109	121	210	327
Pulmonary Minute Volume (cc. air/min.)	3580	4040	4160	6450	3460	3840	4540	8340
Respiratory Rate (per minute)	15	13	27	34	14	16	20	25
Cardiac Rate (per minute)	127	153	139	176	150	151	162	195
Mean Art. Blood Pressure (mm. of Hg)	94	104	103	90	106	109	124	115
Cardiac Output (cc./min.)	3730	5020	3090	4320	2950	3060	4290	6170
Stroke Volume (cc./beat)	29.4	32.8	22.2	24.5	19.7	20.2	26.4	31.6
Total Peripheral Resistance (Absolute Units)	2010	1660	2670	1660	2870	2850	2310	1490
Cardiac Work (calories/min.)	11.4	17.0	10.4	17.0	10.1	10.9	17.3	23.1
Efficiency (%)	17.0	18.7	25.9	18.7	29.8	27.6	18.2	27.4

TABLE 2.—*Mean Cardiodynamic and Energetic Changes of Successive Flow Studies with and without Aminophylline*

	Cor. Flow	O_2 Cons. Heart	Art. O_2 Cont.	Cor. Ven. O_2 Cont.	Cor. A-V Diff. O_2 Cont.	Cor. O_2 Utiliz.	Card. Work	Card. Outp.	Mean Art. B.P.	Rate	TPR (A.U.)	Cor. R (P/F)
Saline Controls												
Before	128	16.3	17.2	4.5	12.7	74.2%	18.0	5160	133	166	2280	1.08
After	123	14.9	16.6	4.4	12.2	73.7%	15.3	4250	137	160	2890	1.16
Change	−5	−1.4	−0.6	−0.1	−0.5	−0.5%	−2.7	−910	+4	−6	+610	+0.08
Drug Action												
Before	105	11.7	14.0	2.9	11.1	79.3%	12.3	3490	108	145	2470	1.06
After	106	12.7	14.3	2.2	12.1	85.0%	17.0	4640	105	169	1920	1.02
Change	+1	+1.0	+0.3	−0.7	+1.0	+5.7%	+4.7	+1150	−3	+24	−550	−0.04
Mean Change Between two series	+6	+2.4	+0.9	−0.6	+1.5	+6.2%	+7.4*	+2060*	−7	+30*	−1160*	−0.12
"t" Values	0.49	1.40	1.34	1.61	2.759	2.446	4.830	5.20	1.07	3.043	4.609	1.601

-Key-

Coronary Flow—cc./100 Gm./min.
O_2 Consumption of Heart—cc./100 Gm./min.
Oxygen Content—vols. %
Cardiac Work—calories/min.
Cardiac Output—cc./min.
Blood Pressure—mm. of mercury
Rate—beats/min.
Total Peripheral Resistance—Absolute Units
Coronary Resistance—MABP/Cor. Flow

* Changes of Statistical Significance.

tent, but this was not large enough to be significant in this small series.

The mean arterial blood pressure showed no remarkable change, but the cardiac rate increased sufficiently to be approaching the level of a significant change. Coronary resistance (expressed as the mean arterial pressure required to force 1.0 ml. of blood through 100 Gm. of myocardium per minute) showed a tendency to decrease, in contrast to control experiments where it increased.

Comment. The most striking effects of aminophylline in these experiments—increases in cardiac rate, output, and work, and a decrease in peripheral resistance—are similar to the findings of other workers.[2, 5, 25] The additional data pertaining to coronary flow and cardiac oxygen consumption suggest that both are increased by the drug, but the latter more so than the former; this indicates that the increase in coronary flow produced by aminophylline, like that of nikethamide,[5] is insufficient to meet the increased oxygen requirements of the myocardium. This conclusion would be firmly established if there were a stable base line from which to measure the drug effects, but the nature of the experiment precludes this. The necessity for an interval of twenty to thirty minutes between the control estimations and the drug administration, the withdrawal of approximately 80 ml. of blood for each period of measurement, the presence of anesthesia by an agent (pentobarbital) which has a relatively brief narcotic effect and the ability to stimulate cardiac rate and output, all tend to produce changes which may simulate, modify, or obscure the effects of the drug. Our attempts to circumvent this difficulty by repeated control estimations without any drug were less successful than anticipated because the absolute values for most of the important functions studied were at a higher level than in the drug experiments; while these discrepancies probably would disappear in a large series of experiments of both types, the obstacles set by the long duration and considerable blood withdrawal would remain.

For these reasons, we decided to attempt to secure valid information on the nature of the effect of aminophylline on the myocardium—whether beneficial or harmful—by a procedure that avoids the necessity for prolonged pauses between observations and for withdrawal of large amounts of blood. The procedure chosen was simple estimation of the coronary arteriovenous oxygen difference.

II. Effect of Aminopylline on the Coronary Arteriovenous Oxygen Difference

Methods. Dogs weighing from 17 Kg. to 27.2 Kg. were anesthetized with 12 mg. per dog of morphine sulfate followed by an intravenous injection of pentobarbital sodium, 30 mg. per Kg. An endotracheal tube was inserted to insure free respiratory exchange; a small catheter within the endotracheal tube was used to deliver a gentle stream of 100 per cent oxygen to the lungs in addition to exchanges of room air during the respiratory depression of early anesthesia. Coronary sinus catheterization was accomplished by the technic of Goodale[14]; a slow drip of heparinized saline (20 mg. heparin in 1 liter of saline) was passed through the catheter. This catheter with drip was connected to a manifold of stopcocks to permit anaerobic collections of coronary venous blood. Arterial puncture was performed and connected likewise to another manifold; this system was originally filled with heparin solution (10 mg. per ml.) to avoid clotting. When arterial samples were not being collected, continuous estimations of mean arterial blood pressure were possible by means of a damped mercury manometer connected to the manifold. Electrocardiographic records were made of conventional limb leads and occasional chest leads.

Approximately one and one-half to two hours after administration of pentobarbital sodium, blood sampling from the femoral artery and the coronary sinus was performed simultaneously at the rate of 1.0 ml. every ten seconds. During the first and fourth minutes of an experimental run, 6.0 ml. samples of blood were collected for controls. Following this, either physiologic saline or Solution Aminophylline U.S.P. (4.0 mg. per Kg.) was injected into a superficial leg vein during a one minute period. Sampling was repeated during the first minute after the injection and every fourth minute thereafter until three or four post-injection samples were obtained.

Blood samples were analyzed for oxygen content by the manometric method of Van Slyke and Neill.[26] Each sample was also analyzed for oxyhemoglobin by the Evelyn colorimetric method,[8] and an estimation of oxygen capacity in volumes per cent made by multiplying the grams of oxyhemoglobin by the factor 1.34. Saturations could then be calculated by the ratio of content to capacity.

Results. Our control experiments with saline injections show a slight variation in the oxygen

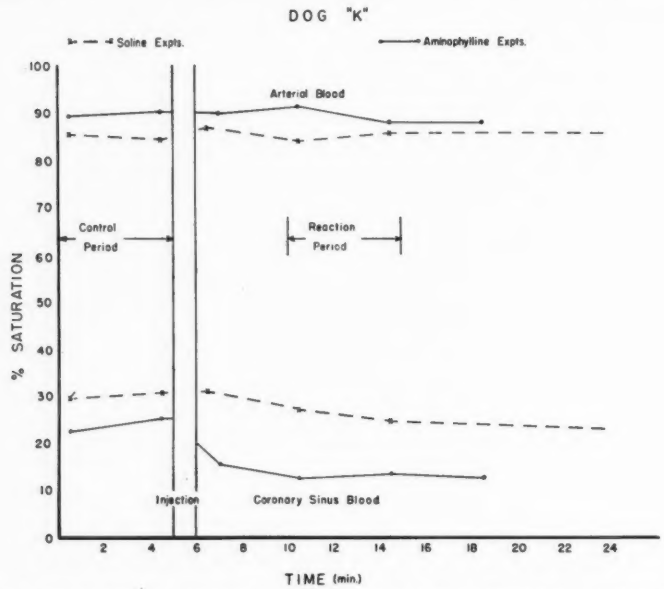

FIG. 1.—Changes in the blood-oxygen saturation of a dog produced by injections of saline and aminophylline.

TABLE 3.—*Changes in Blood Oxygen Saturation*

Dog	Before Injection			After Injection			Change	
	Art.	Ven.	Δ A-V	Art.	Ven.	ΔA-V	Ven.	ΔA-V
Saline Control Experiments								
J	89.4%	38.2%	51.2%	90.2%	34.5%	55.7%	−3.7%	+4.5%
G	95.4	38.3	57.1	93.7	36.8	56.9	−1.5	−0.2
K	85.5	30.3	55.2	85.1	25.7	59.4	−4.6	+4.2
N	90.0	20.1	69.9	91.2	16.5	74.7	−3.6	+4.8
T	88.1	29.5	58.6	90.0	26.7	63.3	−2.8	+4.7
R	92.8	33.4	59.4	94.0	33.8	60.2	+0.4	+0.8
Mean	90.2%	31.6%	58.6%	90.7%	29.0%	61.7%	−2.6%	+3.1%
Aminophylline Experiments								
K	90.0%	24.0%	66.0%	89.1%	13.1%	76.0%	−10.9%	+10.0
H	98.5	29.2	69.3	98.4	18.9	79.5	−10.3	+10.2
J	92.0	49.1	42.9	87.8	26.2	61.6	−22.9	+18.7
G	92.4	30.1	62.3	90.8	18.3	72.5	−11.8	+10.2
M	93.2	20.4	72.8	92.3	11.4	80.9	−9.0	+8.1
P	91.4	26.4	65.0	93.9	20.1	73.8	−6.3	+8.8
R	88.6	25.5	63.1	90.0	17.3	72.7	−8.2	+9.6
S	91.6	36.5	55.1	91.7	15.9	75.6	−20.6	+20.5
Mean	92.2%	30.2%	62.1%	91.8%	17.7%	74.1%	−12.5%	+12.0%

saturation during the sampling periods; a typical result is shown in figure 1. When aminophylline was injected, the coronary venous oxygen saturation fell consistently, and remained at the lower values for varying intervals up to sixteen minutes following the injection.

For comparison, the mean values of the control period and of the period of reaction are tabulated in table 3. The value for the period of reaction was calculated from blood oxygen saturations of samples collected during the fourth and eighth minutes after injection, since A-V oxygen unsaturation would arise by chance less often than once in a hundred trials (see "t" values in table 4).

No attempt was made to estimate cardiac output and work during these experiments; however, observations of changes in blood pressure and pulse rate were suggestive that cardiac work was increased following the injection of aminophylline; 6 of 8 dogs demonstrated a rise in pulse rate and a similar number showed a slight rise in blood pressure during the period of reaction (see table 5).

TABLE 4.—*Mean Changes in Blood Oxygen*

Method	Coronary Ven. O_2		Δ A − Cor. Ven. O_2	
	Content	Sat.	Content	Sat.
Saline Expts.				
Before	5.8 vol%	31.6%	10.8 vol%	58.6%
After	5.4	29.0	11.5	61.7
Mean Change	−0.4 vol%	−2.6%	+0.7 vol%	+3.1%
Aminophylline Expts.				
Before	5.4 vol%	30.2%	10.7 vol%	62.1%
After	3.1	17.7	12.9	74.1
Mean Change	−2.3 vol%	−12.5%	+2.2 vol%	+12.0%
Mean Net Change	−1.9 vol%	−9.9%	+1.5 vol%	+8.9%
"t" Values	3.453	3.885	3.330	4.213

in the drug action experiments these samples represented the period of maximum changes. In six saline control experiments, the mean changes following injection were an increase of 0.5 per cent in arterial oxygen saturation, a decrease of 2.6 per cent in coronary venous oxygen saturation, and hence, an increase of 3.1 per cent in the A-V unsaturation. In eight experiments in which aminophylline was injected, the significant mean changes between the two periods were a decrease of 12.5 per cent in coronary venous oxygen saturation and an increase of the A-V difference or oxygen unsaturation of 12.0 per cent. The mean differences between the two series of experiments are therefore a decrease of 9.9 per cent in the saturation of coronary venous blood and an increase of the A-V unsaturation of 8.9 per cent; these differences are statistically significant when the "t" test for a small series is applied.* The mean differences in the control versus the aminophylline series for both the coronary venous oxygen saturation and the

III. Effect of Aminophylline on Coronary A-V Oxygen Difference in Myocardial Infarction

Since the experiments with normal dogs demonstrated that aminophylline had failed to increase the coronary blood–oxygen supply in relation to cardiac demands, the question immediately arose, whether this same response would be obtained in the infarcted heart of the dog. A small series of animals was therefore prepared and studied.

Methods. Dogs weighing 11 to 22 K. were anesthetized with ether under a closed pressure system, and the heart was exposed by a transthoracic approach. After topical applications of procaine to the myocardium, the major trunk or a branch of the anterior descending coronary artery was dissected free and ligated with silk sutures. The chest was then

* $$\text{"t"} = \frac{\text{difference between means}}{\text{estimated standard deviation}} \times \sqrt{\frac{N_1 \times N_2}{N_1 + N_2}}$$

closed, and the pleural cavity evacuated of air. The animal was then allowed to recover for approximately ninety hours following ligation at which time a catheterization study was performed as described in Part II. Studies on the oxygen saturation of coronary blood were performed before and after aminophylline.

Results. Fourteen animals were subjected to ligation; four died postoperatively. Of the ten surviving operation, two died at time of catheterization studies—one from anesthesia and complicating pleural effusion, and one presumably from ventricular fibrillation during catheterization. Eight dogs survived the study with the results as shown in table 6. Three of these animals were subjected to a second catheterization approximately twenty-eight to thirty-seven days following ligation. All animals were sacrificed within twenty-four hours of the final experiment, and the hearts were studied for pathologic changes.

Five dogs sacrificed during the acute phase of myocardial infarction demonstrated gross necrotic lesions which involved the left ventricular apex, the anterior wall, and the adjacent parts of the septum; approximately 10 to 15 per cent of the total muscle mass of each heart showed infarction. At the time of the drug study, electrocardiograms revealed changes compatible with the diagnosis of acute or subacute myocardial infarction.

Of the three dogs sacrificed in the chronic period of infarction (twenty-eight to thirty-seven days), two dogs (T and P) demonstrated thinning of the left ventricular wall and scarring. The third dog (V) demonstrated a recanalized thrombus in a lateral branch of the anterior descending coronary artery with no gross changes in the myocardium; the electrocardiogram revealed marked RS-T segment elevations and T-wave inversions in Lead I and in the precordial leads at the time of both early and late experiments.

The coronary venous oxygen saturation was observed to fall during the period of four to eight minutes following the intravenous administration of aminophylline in all of the experiments; the mean change in saturation was

TABLE 5.—*Changes in Coronary Venous Oxygen Saturation, Mean Arterial Blood Pressure and Cardiac Rate from Control Period to Reaction Period*

Dog	Cor. V. O_2 Change	Mean Art. Blood Pressure			Cardiac Rate		
		Contr. Pd.	React. Pd.	Change	Contr. Pd.	React. Pd.	Change
Saline Expts							
J	−3.7%	136 mm.	136 mm.	0 mm. Hg	150	150	00
G	−1.5	138	135	−3	100	110	+10
K	−4.6	115	118	+3	130	115	−15
N	−3.6	118	109	−9	175	180	+5
T	−2.8	122	126	+4	170	170	00
R	+0.4	130	130	0	175	175	00
Mean	−2.6%	127 mm.	126 mm.	−1 mm.	150	150	00
Aminoph. Expts							
K	−10.9%	125 mm.	134 mm.	+9 mm.	180	180	00
H	−10.3	118	122	+4	118	130	+12
J	−22.9	131	140	+9	130	165	+35
G	−11.8	112	127	+15	110	145	+35
M	−9.0	124	132	+8	170	195	+25
P	−6.3	155	152	−3	130	150	+20
R	−8.2	145	140	−5	180	180	00
S	−20.6	125	127	+2	150	165	+15
Mean	−12.5%	129 mm.	134 mm.	+5 mm.	145	165	+20

a decrease of 9.2 per cent from a level of approximately 30 per cent. The arterial saturation was less stable than in the normal dogs, and two dogs showed a moderate decline of arterial saturation during the experimental period. The A-V difference or oxygen unsaturation was increased by aminophylline in seven of the eight acutely infarcted hearts; the mean change was an increase of 6.6 per cent from levels of approximately 60 per cent unsaturation. These changes are in the same direction as those which followed the intravenous injection of aminophylline in dogs with normal hearts.

IV. Effects of Nitroglycerin on Coronary Venous Oxygen Saturation in Normal Dogs

When we found that the results of intravenous aminophylline injections were rather uniformly opposite to the anticipated reactions of an ideal coronary vasodilator, we thought it worth while to make similar observations with nitroglycerin, which enjoys long standing clinical approval.

Methods. The same procedure was followed as in Part II except that no saline experiments were performed; data needed for comparison to the saline experiments were taken from the results of Part II. A solution of nitroglycerin which was freshly prepared by diluting U.S.P. tablets, injection, in saline was injected for the drug study.

Table 6.—*Changes in Blood Oxygen Saturation*
Aminophylline in Infarcted Hearts

Dog	Before Injection			After Injection			Change	
	Art.	Ven.	Δ A-V	Art.	Ven.	Δ A-V	Ven.	Δ A-V
Acute Phase								
A′	73.7%	23.3%	50.4%	74.8%	21.6%	53.2%	−1.7%	+2.8%
H	95.5	31.7	63.8	94.5	22.3	72.2	−9.4	+8.4
T	83.9	26.8	57.1	79.1	14.5	64.6	−12.3	+7.5
P	87.8	22.0	65.8	80.2	14.7	65.5	−7.3	−0.3
V	97.3	46.2	51.1	91.4	33.2	58.2	−13.0	+7.1
W	93.0	30.4	62.6	93.1	20.5	72.6	−9.9	+10.0
X	95.9	40.3	55.6	95.4	27.0	68.4	−13.3	+12.8
Y	92.9	21.8	71.1	90.8	15.4	75.4	−6.4	+4.3
Mean	90.0%	30.3%	59.7%	87.4%	21.1%	66.3%	−9.2%	+6.6%
Chronic Phase								
T	96.4%	31.0%	65.4%	96.3%	20.7%	75.6%	−10.3%	+10.2%
P	92.9	37.9	55.0	91.6	23.0	68.6	−14.9	+13.6
V	98.0	44.8	53.2	100.0	28.6	71.4	−16.2	+18.2
Mean	95.8%	37.9%	57.9%	96.0%	24.1%	71.9%	−13.8%	+14.0%

These changes in oxygen saturation were not accompanied by an elevation in blood pressure which was observed at a mean level of approximately 86 mm. Hg pressure. There was a small increase in pulse rate of 5 beats per minute from a mean rate of 123 beats per minute.

The three animals in which a second drug study was performed in the chronic stage of infarction showed a more marked fall in coronary venous oxygen saturation and the response in general was more like that of the normal dogs.

Results. In the first two experiments with nitroglycerin, 0.3 mg. of the drug was injected intravenously over a period of one minute. This dosage barely produced a 5 mm. Hg fall in the mean arterial blood pressure but was associated with cardiac acceleration of approximately 40 beats per minute in the immediate

postinjection period. Since the coronary venous saturation did not rise more than 5 per cent in the same period, it seemed advisable to use a larger dosage.

Six animals were studied with a dosage of 0.6 mg. of nitroglycerin injected intravenously. A period of one minute was again used for the injection time. The most significant change in the coronary venous saturation occurred during the first minute which followed the completion of the injection; at this time, a mean rise of 10.7 per cent in the coronary venous oxygen saturation was observed from a mean control level of 25.0 per cent. The coronary A-V difference or unsaturation decreased from 60.3 per cent to 48.7 per cent. When compared with the changes in the saline control experiments for the same postinjection period, the difference between the two mean changes is highly significant. See table 7.

TABLE 7.—*Changes in Blood Oxygen Saturation*

Nitroglycerin Expts.

Dog	Before Injection			1st Min. after Inj.			Change	
	Art.	Ven.	Δ A-V	Art.	Ven.	Δ A-V	Ven.	Δ A-V
C′	83.9%	26.8%	57.1%	82.5%	45.9%	36.6%	+19.1%	−20.5%
D′	75.8	32.6	43.2	77.6	40.0	37.6	+7.4	−5.6
F′	88.2	21.8	66.4	86.7	34.8	51.9	+13.0	−14.5
G′	85.1	14.9	70.2	85.9	20.2	65.7	+5.3	−4.5
H′	88.1	23.5	64.6	86.1	43.0	43.1	+19.5	−21.5
J′	90.7	30.5	60.2	87.8	30.2	57.6	−0.3	−2.6
Mean	85.3%	25.0%	60.3%	84.4%	35.7%	48.7%	+10.7%	−11.5%
Mean Saline Expt.	90.2	31.6	58.6	91.2	30.4	60.8	−1.2	+2.2
Mean Net Change							+11.9%	−13.7%

The mean arterial blood pressure before the injection of nitroglycerin was 144 mm. Hg; during the injection the mean maximum drop was 26 mm. Hg, but by the end of the first collection period (one minute following the completion of the injection), the blood pressure had recovered to a level only 7 mm. Hg below the mean control level. Between five and eight minutes after injection, the blood pressure had returned to a mean level of 141 mm. Hg.

The injection of nitroglycerin was also accompanied by an increase in cardiac rate; from a control level of 137 beats per minute, the pulse increased to 191 per minute during the injection. During the first collection period, it was slightly lower at 180 beats per minute; by the fifth to eighth minutes after injection, the pulse had reached a mean level of 152 beats per minute.

In comparison with aminophylline, nitroglycerin produced the opposite change in the coronary venous oxygen saturations and the estimated tensions; the increase in the coronary venous blood oxygen saturation with nitroglycerin occurred in the period in which blood pressure was effectively reduced and presumably when cardiac work was decreased. Aminophylline decreased the coronary venous oxygen saturation, and this occurred at the time when blood pressure was increased and presumably when cardiac work was increased.

DISCUSSION

Drugs which have been shown in laboratory preparations to have vasodilating properties for the coronary circulation may be roughly divided into two groups: (a) those which in addition to their vasodilating properties, also have stimulating effects upon the myocardium and thereby increase cardiac work; (b) those which also tend to decrease the work of the heart which is chiefly accomplished by peripheral vasodilatation with decreased peripheral resistance. Aminophylline and nikethamide are examples of the former group while the nitrites are the chief example of the latter.

The heart seems to follow Barcroft's dictum that there cannot be an increase in activity of an organ without an accompanying increase

in oxygen uptake[4, 13, 17, 23]; an ideal coronary vasodilator should therefore increase coronary flow, decrease cardiac work, or at least increase oxygen supply to the myocardium in excess of the increase or change in oxygen demand. At present the closest approach to this ideal is found in the nitrites.

The use of aminophylline, a cardiac stimulant, to obtain an increase in coronary circulation has been given considerable clinical trial, but there is lack of agreement as to its effectiveness[1, 2, 3, 7, 9–12, 18, 19, 21, 22, 24, 27–29]; this disagreement obviously results from the difficulty of obtaining adequate and simple objective measurements of coronary flow in man.

Under the conditions of the experiments with intact anesthetized dogs, our findings reported in Part I indicate that there was no significant increase in mean flow in spite of an increase in work of the heart; this suggested that the myocardium was less well oxygenated for increased work levels resulting from the injection of the drug aminophylline. The findings in Parts II and III strengthen this belief. The intravenous injection of aminophylline lowered the coronary venous oxygen saturation and tension in the normal dog heart and in the heart with myocardial infarction; this reflects the failure of oxygen supply to meet the oxygen demand. Although work was not measured directly, changes in blood pressure and cardiac rate suggested that the same stimulant action which was observed and measured in the first group of experiments increased cardiac activity in the study of coronary venous blood oxygen changes. It thus appears that aminophylline does not improve oxygenation, but that it intensifies the existing tissue demands for oxygen in excess of the supply provided by the coronary blood flow. This appears to be true both in the normal and infarcted heart of the dog.

With these findings, it is of interest to speculate whether the infarcted zone is responsive to the stimulating properties of aminophylline. If the infarcted area is viable to any degree and capable of responding to stimulation, it seems unlikely that an augmented flow could be produced by aminophylline without increasing myocardial metabolism and oxygen demands. If the infarcted zone is nonresponsive, it is possible that it may benefit indirectly by increased flow in collateral channels. These local metabolic changes within the infarcted zone seem to be of sufficient importance to warrant further investigations which are being considered.

Summary

The effects of intravenous aminophylline on the coronary circulation with special reference to the oxygen requirements of the heart were studied by methods of catheterization in intact anesthetized dogs with normal and infarcted hearts.

By use of the nitrous oxide method of measuring the coronary blood flow, no significant change in coronary blood flow was observed following the injection of clinical doses of aminophylline in normal dogs; this failure to increase flow was reflected in an increased coronary A-V oxygen difference and accompanied by increases in cardiac work and oxygen uptake.

A second series of experiments, designed to demonstrate the failure of aminophylline to increase oxygen delivery to satisfy oxygen requirements, was performed with catheterization of the coronary sinus and blood-oxygen saturation studies. Following injections, the coronary A–V unsaturation in normal dogs increased 12 per cent; this occurred with a lowering of the coronary venous oxygen saturation and estimated oxygen tension. A lowering of 9 per cent saturation in coronary venous saturation occurred in animals with infarcted hearts following administration of the drug; this was observed with a 6.6 per cent increase in the coronary A–V oxygen difference.

In contrast, intravenous nitroglycerin in normal hearts effectively raised the oxygen saturation of coronary venous blood by 11.9 per cent during the phase of maximal depression of blood pressure.

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Blood Vessels of the Skin in Chronic Venous Insufficiency

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This study concerns an evaluation of the anatomicopathologic changes found in blood vessels of the skin in areas of venous insufficiency in the lower legs. These changes have been compared with the vascular structure in comparable areas of skin in normal persons. Apparently evidence of arteriolar damage is more a concomitant finding in the clinical picture of chronic venous insufficiency than are venular changes. This is demonstrated in a study of 30 patients. The vascular changes show no correlation with the condition of the skin at the site from which the biopsy material was taken.

THE BASIC problem which was studied in this investigation may be stated as follows: In patients who show clinical evidence of chronic venous insufficiency, do the blood vessels of the skin in areas of venous insufficiency differ from those in comparable areas of skin in normal persons and, if so, what is the qualitative nature of the changes?

Specimens of skin were obtained from the lower part of the leg in a group of patients in whom a diagnosis of chronic venous insufficiency had been made. Specimens of skin from comparable areas in apparently normal persons (that is, normal from the standpoint of there being no evidence of any peripheral vascular disease) were then obtained for comparison. The group of patients with "chronic venous insufficiency" was carefully screened to exclude all persons who did not present very definite clinical evidence of venous insufficiency, such as varicose veins, edema following thrombophlebitis, or brawny induration.

The material for study was obtained from specimens for biopsy from patients in the Section on Dermatology and Syphilology and from sections of skin taken at the site of incision (in the region of the ankle) in patients who underwent operation for treatment of varicose veins. Control material was obtained in cases in which necropsy was performed and in which there was no history of peripheral vascular disease or arterial hypertension. These specimens were obtained from comparable sites to those of the cases of chronic venous insufficiency and from persons in approximately the same age range.

A detailed clinical analysis of the patients included in this study is being given elsewhere[1] and will be but briefly mentioned here. Sixteen control specimens of skin were obtained, 10 of which were from men and 6 from women. The oldest patient was 85 and the youngest 16 years of age.

Thirty-one specimens of skin were obtained from 30 patients for whom a clinical diagnosis of chronic venous insufficiency had been made. Of these, 14 were men and 16 women. The oldest was 76 and the youngest 24 years of age.

HISTOPATHOLOGIC STUDIES

The epidermal and dermal changes (other than those involving the blood vessels) will not be reported in detail, inasmuch as they have been well described by Gans.[2] Other than this description by Gans and a study of a single tissue specimen from a varicose ulcer reported by Golden,[3] no description of the cutaneous vascular changes associated with chronic venous insufficiency has been found in a search of the literature. It is assumed, therefore, that this investigation represents the first detailed description of the changes in the arterioles and venules of the skin in this condition.

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Abridgment of thesis submitted by Dr. Kulwin to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

Method

The tissue specimens were fixed in formalin and blocked in paraffin. Three stains were used on the specimens—hematoxylin and eosin, elastin H,[4] and Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain,[5] hereinafter referred to as the ELVG stain. The problem of whether vascular structures are altered in size during fixing processes has been raised, but, inasmuch as the control specimens were processed in an identical manner, any such phenomenon is a constant factor and as such can be discounted. It has been shown[6] that physiologic constriction or dilatation of the vessels is not rendered permanent by fixation of tissue.

Since at least six to eight sections of each specimen were studied for evidence of vascular changes, it is felt that the possibility of having missed changes which were present is slight.

In this investigation, attention was concentrated on the vessels at the dermosubdermal junction, first, to establish a degree of uniformity in the size of the vessels studied, and second, because blood vessels smaller than those found at this level could not always be definitely identified as arterioles or venules.

Pathologic Findings

Control Group. Of the 16 control specimens, abnormal vessels were found in only one, which was taken from skin on the leg of a man 63 years of age, who had died of carcinoma of a kidney and metastatic growths. The arterioles in this section showed marked intimal proliferation. In the other 15 control specimens the appearance of the arterioles and venules conformed to the descriptions in standard textbooks of histology. Representative vessels from normal control subjects are illustrated in figures 1 and 2.

FIG. 1 (*left*).—Normal cutaneous arteriole from leg of man aged 56 years. (ELVG stain, ×275).
FIG. 2 (*right*).—Normal cutaneous venule (with branches) from leg of woman aged 48 years (ELVG stain, ×110).

Group With Chronic Venous Insufficiency. (1) Arteriolar Changes: Of 30 biopsy specimens in which the arteriolar structure could be observed 5 showed no pathologic change, and 25 showed variations from the normal. Of the 5 specimens which showed no evidence of arteriolar damage, 4 were from areas of dermatitis and one was from normal skin; 3 of these pa-

tients had no evidence of cardiovascular disease, one had mild arterial hypertension (150 mm. of mercury systolic and 90 diastolic), and in one patient no blood pressure determination was made.

The 25 specimens which showed arteriolar pathologic change were considered from the standpoint of changes in the intima, the internal elastic membrane, the endothelium, and the media, in that order. No single specimen in this group showed pathologic changes in all of these structures.

Intimal proliferation was seen in 16 of the 25 specimens which showed arteriolar changes, in 2 of which elasticization of the intima was also seen, and no intimal change was seen in 9. Two of the specimens without intimal changes were from hypertensive patients and 4 of the specimens with intimal changes were from patients with definite arterial hypertension. Of the 16 specimens which showed intimal damage, 8 were from areas of ulceration, 6 from areas of dermatitis, and only 2 were from normal skin.

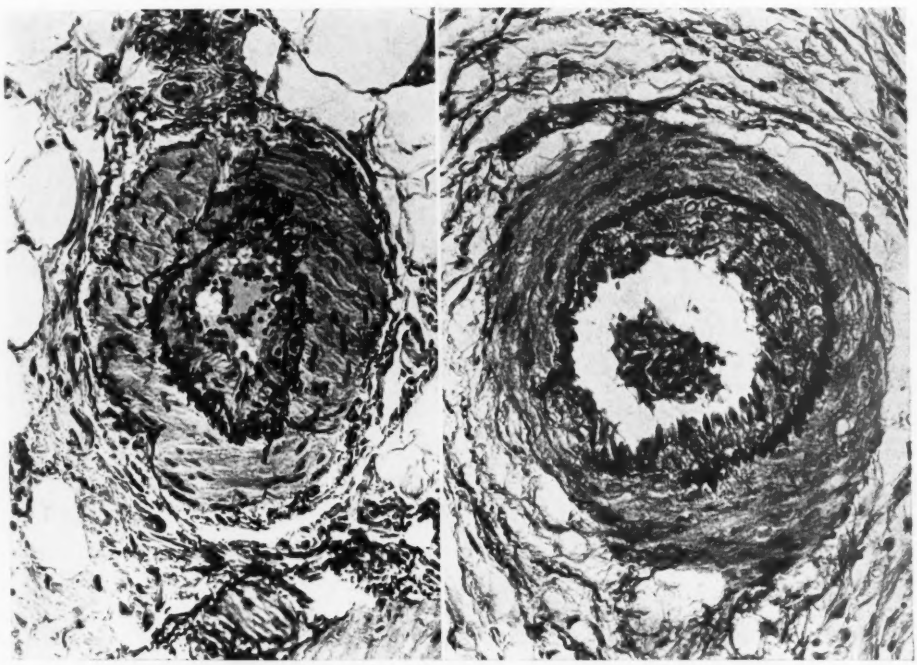

FIG. 3 (*left*).—Cutaneous arteriole from leg of a woman aged 75 years who had had induration and edema of both legs for approximately fifty-five years. Blood pressure 160 mm. of mercury systolic and 80 diastolic. Note the intimal proliferation and elasticization as well as thickening of the medial layer of the vessel wall (elastin H stain, ×200).

FIG. 4 (*right*).—Cutaneous arteriole from leg of a man aged 24 years who had had thrombophlebitis of the left iliofemoral vein following an operation three years previously. Subsequently, varicose veins developed on the left leg. Blood pressure 114 mm. of mercury systolic and 80 diastolic. This section shows intimal proliferation, a normal internal elastic membrane, and hypertrophy of the medial coat (elastin H stain, ×285).

The internal elastic membrane appeared normal in 22 specimens of 29 in which this structure was examined, and showed evidence of fragmentation or reduplication or both in 7. In all 6 patients in this group of 25 (with arteriolar changes) who had arterial hypertension (in addition to chronic venous insufficiency), the internal elastic membrane appeared normal. Of the seven specimens which showed evidence of damage to the internal elastic mem-

brane, three were from areas of ulceration, and two each from areas of dermatitis and of normal-appearing skin

Endothelial hyperplasia was seen in 4 specimens, two of which were from hypertensive patients; of these 4 specimens, two were from ulcerated sites, and one each from normal skin and from areas of dermatitis.

The medial coat of the arterioles was thickened in twenty-one specimens of the twenty-nine in which this coat could be observed and normal in eight. Five of the hypertensive patients showed this change and one did not. The condition of the skin in these twenty-one biopsy specimens was as follows: seven ulcerated, 6 dermatitis, and 8 normal.

Complete obliteration of the arterioles was seen in 3 specimens, all of which were from ulcerated areas. None of these patients was hypertensive.

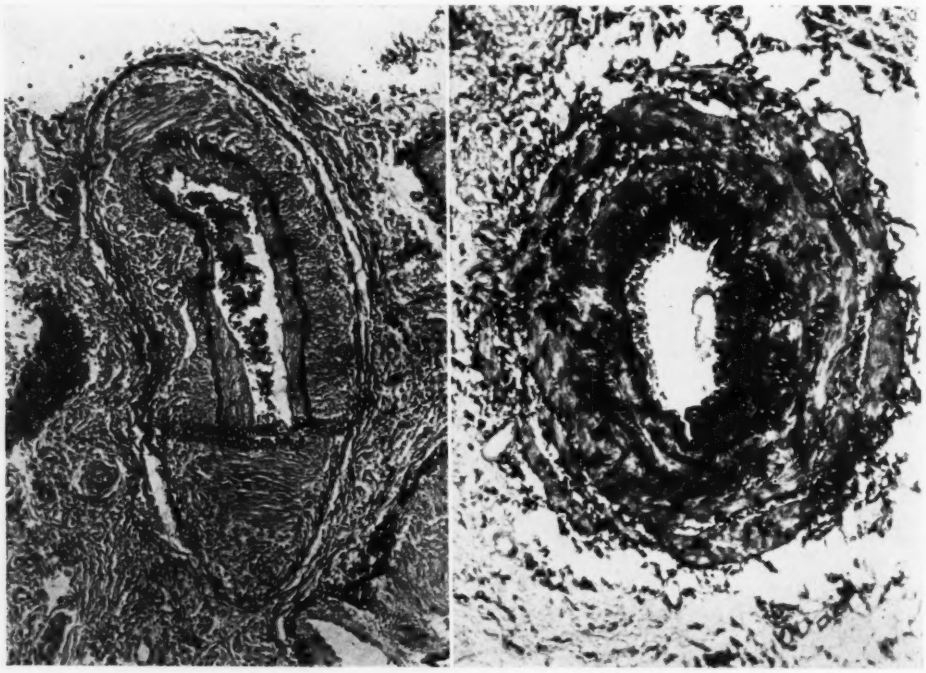

FIG. 5 (*left*).—Arteriole in skin from leg of a man aged 31 years who had had episodes of induration and edema of both legs for one and a half years without a definite antecedent history of thrombophlebitis. Blood pressure 126 mm. of mercury systolic and 86 diastolic. Intimal proliferation, reduplication of the internal elastic membrane and medial hypertrophy are seen in this section (elastin H stain, ×95).

FIG. 6 (*right*).—Cutaneous venule from leg of a man aged 36 years. This patient had had a crushing injury to the left leg six years previously, and postpneumonic thrombophlebitis of the left iliofemoral vein nine months previously; immediately after the latter episode bilateral varicosities developed. Blood pressure 125 mm. of mercury systolic and 74 diastolic. This section shows endothelial hyperplasia and a very pronounced degree of medial hypertrophy with a laminated appearance of the media (ELVG stain, ×75).

(2) Venular Changes: Of 30 specimens in which the structure of the venules was studied, 15 were normal. Eight of these specimens were taken from areas of dermatitis, 3 from ulcerations and 4 from normal-appearing skin.

Changes in the venules were classified as intimal, endothelial and medial. Only one specimen showed changes in all three structures.

Six specimens showed intimal proliferation, 3 showed endothelial hyperplasia, and 13 showed broadening of the medial layer. Of the 15 sections which showed venular changes, 4 were from areas of dermatitis, 6 from ulcers and 5 from sites of normal skin. Three specimens showed complete venular occlusion; these were all from ulcerated areas.

Figures 3 to 5 illustrate representative arteriolar changes which were seen in this study, and figure 6 illustrates typical venular changes.

Comment

The fact that of the 25 specimens that showed arteriolar changes, 8 were from areas of normal-appearing skin indicates that the arteriolar changes are not necessarily secondary to inflammatory changes in the skin and subcutaneous tissue. Also, of the 8 patients in this series with chronic venous insufficiency and normal skin, only one showed no evidence of vascular pathologic changes.

The thickening of the medial arteriolar coat found in 21 specimens (only 5 of which were from patients with arterial hypertension) is not too dissimilar from that seen in hypertensive arteriolar disease.

Of 16 specimens which showed intimal hyperplasia of the arterioles, 14 were from areas of cutaneous changes (dermatitis or ulceration or both) and only 2 were from normal cutaneous sites. It appears that this finding might bespeak the role played by cutaneous lesions in the production of intimal vascular pathologic changes, as has been suggested.[7, 8]

Since venular changes were found in only 15 of 30 specimens studied, it would seem that no definite conclusions can be drawn as to their significance.

Detailed studies of capillary structures were not included in this investigation. It was noticed, however, in the process of reviewing these sections of skin, that a large number of specimens showed evidence of capillary dilatation and proliferation, particularly in the upper portion of the cutis in lesions of long duration.

Summary and Conclusions

The anatomicopathologic features of the blood vessels of the skin in 31 biopsy specimens from 30 cases of chronic venous insufficiency of the lower extremities have been studied.

Twenty-five specimens, 8 of which were of normal-appearing skin, showed evidence of arteriolar damage in the form of intimal proliferation, fragmentation or reduplication, or both, of the internal elastic membrane, endothelial hyperplasia, medial hypertrophy, or some combination thereof.

Fifteen specimens showed evidence of venular pathologic changes in the form of intimal proliferation, endothelial proliferation and hyperplasia, medial hypertrophy, or some combination thereof. Five of these specimens were of normal-appearing skin.

Pathologic changes in the arterioles of the skin are a usual concomitant finding in areas of chronic venous insufficiency of the lower extremities. Changes in the venules exist in about one-half of the cases. The causal relationship of these changes to cutaneous manifestations of chronic venous insufficiency has not been determined.

Acknowledgments

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Effect of Potassium and of Desoxycorticosterone Acetate in Acute Heart Injury in the Rat

By CHARLES G. CAMPBELL, M.D., M.Sc., AND SYDNEY M. FRIEDMAN, M.D., PH.D.

The rat myocardium was injured by means of a hot probe applied to the exposed surface of the left ventricle and the sequence of electrocardiographic changes was studied. Administered potassium as potassium chloride aggravated the electrocardiographic changes, while the administration of DCA improved the cardiographic picture. It is suggested that the beneficial action of DCA may be due to its plasma potassium lowering effect.

IN RECENT years, a considerable volume of information has accumulated regarding the cardiac effects of alterations in the extracellular potassium concentration. As the potassium concentration rises there is a sequence of electrocardiographic changes characterized by an increase in the height of the T wave, a disappearance of the P wave, a broadening of the QRS complex and finally, cardiac arrest in diastole.[1–4] In contrast, a diminution in the potassium concentration is reflected mainly in a flattening of the T wave.[5–8]

While the marked effects of variation in potassium concentration on cardiac function seem to be well established, there is no settled opinion as to the fate of cardiac potassium in heart disease. It has been shown that in some types of chronic heart disease the myocardial tissue loses potassium,[9, 10] but whether this is an additional handicap is not definitely known. Evidence has also been sought regarding changes in potassium concentration or distribution in acute myocardial infarction, but thus far the data are inconclusive.[11–14]

It seemed to us of some importance to obtain further evidence regarding the role of potassium in acute focal cardiac damage. Presumably, necrosis of cardiac muscle, like that of skeletal muscle[15] releases considerable amounts of potassium. While this would be of little importance in the necrotic area itself, the potassium might well accumulate in the adjacent partially damaged area and interfere with the action potentials developed in this area. Thus, the potassium liberated from the necrotic zone might further impair the function of a comparatively large segment of heart muscle. Furthermore, it has been shown by Selye[16] that in the alarm phase of the general adaptation syndrome there is a tendency towards an accumulation of serum potassium. The acute development of an area of cardiac necrosis might certainly be expected to act as an alarming stimulus. Consequently, it might be argued that there is not only a local accumulation of potassium adjacent to the necrotic area, but also a general accumulation of this ion as a result of the nonspecific effects of sudden damage.

It seemed to us that such a disturbance in potassium as here postulated could be studied indirectly. Thus, the electrocardiographic response of animals with acute myocardial damage might be expected to become aggravated in the presence of administered potassium, while improvement might follow treatment aimed at accelerating the removal of potassium.

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METHODS

Albino rats were used throughout and methods were accordingly adapted to this species.

The electrocardiograph. A string galvanometer with the modifications described by Rappaport and Rappaport[17] was used. With this equipment, Lead I is sometimes very small, owing to the vertical position of the rat heart, and rotation of the animal to right or left changes the amplitude of the complexes in this lead. To overcome these drawbacks a tilt-board was designed. The skin web between digits was pierced by a sharp surgical needle attached to the center of each silvered electrode plate, and jelly was also applied. This method of contact reduced electrical interference to a minimum. The animal's incisors were hooked under a metal arc at the head of the board and the tail drawn through a hole at the base and transfixed. This ensured rigidity of the animal's

posture, especially since the line of the spine was maintained by a ridge along the center of the board. The whole board was then tilted to the left and supported at an angle of 70 degrees. This maneuver throws the heart into a more horizontal position and Lead I yields a readable, fairly constant configuration approximating that of man.

In order to avoid the variable effects of the animal struggling on the board, Evipal sodium was selected as anesthetic. Evipal is fast in action, short-lived and, in the doses used (10 mg. per 100 Gm. intraperitoneally in the male, 9 mg. in the female) is apparently without effect on the heart, as determined by the uniformity of repeated tracings on different occasions.

Myocardial damage. Local damage to the myocardium was produced by a hot probe. With the animal under Evipal anesthesia, an incision was made through the shaved skin 1 cm. to the left of the sternum. Pectoral muscles were separated and the ribs exposed. The left chest wall was then incised and opened. Care was taken in spreading the incision open not to tear through the fine pleuropericardial membrane separating the right from the left pleural cavity.

A round probe with a flat tip 1 mm. in diameter was then rapidly heated to red in an open flame and applied to the left ventricle near the tip. The wound was then closed rapidly and the pleural cavity aspirated. With this technic, the chest was never open longer than one and one-half minutes and the mortality in 65 operations was only 3 per cent.

Experiments

The range of normal variation in the electrocardiogram. The range of variation in the electrocardiographic tracing in 21 representative animals was first studied. There was some slight respiratory variation in the amplitude of the deflections particularly in S_3. Left axis deviation was not seen, the T wave was never inverted or depressed, and only occasionally was a small Q wave seen. The rhythm was always regular.

Repeat tracings obtained in these animals during a one month period showed only minor variations in the amplitude of the different deflections.

Some chest leads were also taken on these animals by the use of a small manual electrode with a contact plate 4 mm. in diameter connected directly to the left arm plate. For this lead, the left forelimb of the animal was not connected and the amplifier connections of left arm and left leg were switched. The exploring electrode was applied with jelly to the shaved chest. The electrode placed about 1 cm. to the left of the xiphisternum yielded a highly variable pattern. This was to be expected in view of the relative size of electrode and heart. In this study of myocardial injury, however, it became important to use "Lead IV" to reinforce the findings in the standard first lead, especially since sharp inversion of the T wave in Lead IV never occurred spontaneously in the normal animal, although the S-T segment and T wave in this lead were sometimes slurred below the line.

Experiment 1

This experiment was designed as a preliminary study of the effect of thoracotomy and of myocardial damage on the electrocardiogram and on the plasma potassium concentration.

Twenty-six male albino rats of an inbred Wistar strain, weighing approximately 250 grams each, were divided into three groups. Group I, consisting of 10 animals, served as untreated control. The 8 animals of Group II were subjected to a sham thoracotomy operation. The 8 animals of Group III were subjected to myocardial injury according to the method described. All animals received Purina Fox Chow and water ad libitum.

Electrocardiographic tracings were obtained in all animals on the day preceding operation and again on the first, second, and third postoperative days. By the second or third postoperative day electrocardiographic evidence of myocardial injury was maximal. Blood was taken on the third day by heart puncture for the determination of plasma potassium according to the method of Polley.[18] The animals were then killed and the gross appearance of the heart noted before fixation. Sections of heart were then stained with hematoxylin and eosin and examined microscopically.

Electrocardiograms. No change was observed in the tracings obtained in Group I, the control animals, which were examined on four occasions in the experiment. Similarly, Group II, subjected to a sham operation, showed no abnormalities except in 2 cases. Autopsy of these 2 animals showed that the heart had been caught in suturing the thoracotomy wound.

Electrocardiographic evidence of injury was clearly apparent in the tracings of Group III. The changes observed could be divided into two categories, those which were definite or marked and those which were slight or suggestive. It seemed to us that a distinct and constant inversion of the T wave in Lead I (and often T_4 as well) represented a marked change (fig. 1), while minor changes in Lead I with supporting changes in Lead IV could be considered as slight or suggestive.

Four of the 8 animals in Group III of this experiment showed definite changes, while 3 showed suggestive changes. The eighth animal in this group showed no electrocardiographic evidence of the damage inflicted.

Pathologic examination. At autopsy, all animals showed about the same degree of epicardial injury. There was a white spot about 1.5 mm. in diameter surrounded by zones of purplish or reddish discoloration. Microscopically, there was a fairly deep arc of necrotic muscle surrounded by a reactive zone. There was a variable degree of pericarditis present which may have contributed to the electrocardiographic pattern.

Plasma potassium. Analysis of plasma samples obtained on the third postoperative day revealed no difference in the plasma potassium levels of the three groups.

Experiment 2

As a result of the first experiment it became feasible to study the effect of administered potassium and of measures tending to reduce the plasma potassium concentration in animals with a myocardial injury.

Thirty female albino rats of the Sherman strain, weighing approximately 120 grams, were divided into four groups. Group I, consisting of 7 animals, served as untreated control, while the 7 animals of Group II were subjected to myocardial injury as described above. Group III consisted of 8 animals subjected to myocardial injury and given added potassium, while the 8 animals of Group IV received desoxycorticosterone acetate (DCA) as treatment following the injury.

In preliminary experiments in animals of this weight it had been determined that the intraperitoneal administration of 1.2 per cent potassium chloride (approximately isotonic) temporarily elevated the plasma potassium concentration by 3 to 4 mEq., an elevation which itself did not cause marked electrocardiographic changes. Similarly, it had been determined that the administration of 3.1 per cent potassium citrate for twelve days as

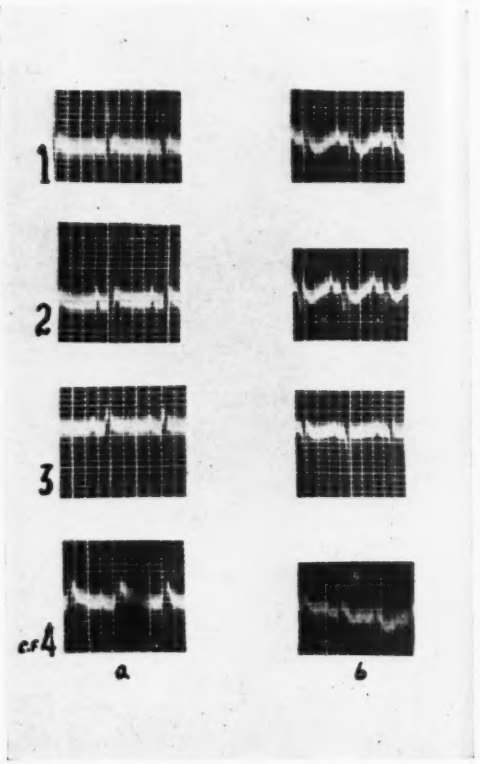

FIG. 1.—Definite electrocardiographic changes after injury. (a) Control. (b) Second post-operative day. Note Q waves and inversion of the T wave in Leads I, II, and IV.

drinking water to such animals elevated the plasma potassium level about 1.5 mEq. without electrocardiographic changes. In view of these findings, the animals of Group III received additional potassium by the intraperitoneal injection of 3 cc. of 1.2 per cent potassium chloride three times a day postoperatively at six hour intervals, while 3.1 per cent potassium citrate was substituted for their drinking water.

Among its many other effects, DCA is known to lower the plasma potassium concentration. For this reason it was administered to the animals of Group IV. Three one-third portions of a 75 mg. Cortate pellet were separately implanted subcutaneously in each animal at the time of operation.

An electrocardiographic tracing was taken each day for three days postoperatively in all animals. Blood samples were taken by heart puncture on the third postoperative day, about six hours after the last potassium chloride injection, following which the animals were killed.

Table 1 presents the essential findings. Electrocardiographic changes are denoted as definite or suggestive, according to the criteria stated for the preceding experiment. For convenience in assessing results the pathologic changes were graded plus 1 to plus 4.

TABLE 1.—*Electrocardiographic Findings and Plasma Potassium Levels in Control and Injured Untreated Rats and on Injured Rats Given Potassium Chloride and DCA*

Group	1	2	3	4
Treatment	Control	Injured	Injured + KCl	Injured + DCA
No. of animals	7	7	8	8
ECG changes:				
definite		3	6	2
suggestive		1	1	0
none	7	3	1	6
plasma K in mEq	4.95	5.03	4.74	3.37
	(3.87–6.00)	(3.37–6.25)	(3.87–6.6)	(2.5–4.4)

The untreated control group showed neither electrocardiographic abnormality nor cardiac pathology.

Four of the 7 untreated injured animals of Group II developed electrocardiographic evidence of injury. In contrast, 7 of the 8 animals in Group III, given added potassium, developed changes. On the other hand, only 2 of the 8 animals in Group IV, given DCA, showed cardiographic evidence of damage. The degree of injury and pericarditis in the three groups was closely comparable.

The plasma potassium concentration was altered only in the group treated with DCA. Here the treatment was quite effective in lowering the plasma potassium within the three-day period. It should be pointed out that despite the lack of an altered plasma potassium level in Group III, these animals were probably subjected to transient elevations in the quantity of circulating potassium.

One animal in Group III and one in Group IV succumbed as a result of gross infection. This factor was controlled in the third experiment of the series by the administration of penicillin.

Taken as a whole, this experiment suggests that a high potassium intake adversely affects the injured myocardium as measured by the electrocardiogram. In the potassium-treated group, not only did more animals develop electrocardiographic changes (7 out of 8) in contrast with the control injured group, but also more showed a marked change (6 out of 8) even when the injury and pericarditis were not especially severe. This finding is in agreement with the observation of Sharpey-Shafer[19] that in man the administration of potassium exaggerated the pattern of infarction and increased the inversion of the T wave. These results contrast with the observation that only 2 of the 8 DCA-treated animals in which the potassium level was lowered developed an altered electrocardiographic pattern.

Experiment 3

This experiment was designed to enlarge upon the effect of DCA treatment on the damaged heart by using a larger series of animals. Penicillin was used to control the variable of infection, and an attempt was made to produce a more severe injury so that a beneficial effect of DCA might be more easily observed.

Thirty-eight male albino rats of an inbred Wistar strain, weighing approximately 100

grams each, were divided into three groups. Group I, consisting of 6 animals, served as untreated control. The remaining 32 animals were subjected to myocardial injury, half of these (Group II) receiving no treatment and half (Group III) receiving DCA treatment postoperatively as described in the previous experiment. In applying the hot probe to the region of the apex of the heart an effort was made to secure a greater degree of injury than previously by holding the probe against the heart for a longer period.

In the week previous to operation, 4-lead electrocardiograms were taken on all 38 animals. Three hours before operation all these animals received subcutaneously 6000 units of procaine penicillin in 2 per cent aluminum monostearate diluted in sesame oil.

Following operation, 4-lead tracings were obtained from all injured animals on the first, second, third, fourth, and sixth postoperative days. Table 2 presents the findings, using the criteria previously described.

Two animals in Group II, the untreated injured group, died during the course of the experiment. In one, the only ascertained cause of death was the myocardial injury. The second animal succumbed some time after an Evipal injection, although the dose used had previously been well tolerated.

Electrocardiograms. No changes were observed in the control group.

In Group II, injured and without subsequent treatment, all 16 animals showed electrocardiographic evidence of damage. Of these 14 showed the marked type of change.

Of the 16 animals receiving DCA, Group III, 14 showed electrocardiographic changes. Ten of these were of the marked type. Again the degree of injury and pericarditis in the two injured groups was closely parallel.

In this experiment the animals were followed for six days so that it was possible to observe their progress which, in many cases, tended toward electrocardiographic recovery. Since changes in the T wave in Lead I and the S-T segment in Lead I afforded the best electrocardiographic evidence of damage, it was felt that a tracing could not be considered normal until these segments were within the normal range. Although T_1 was often small and to some extent variable it was never found below the isoelectric line in the normal. A tracing was therefore considered to have become normal when the affected T_1 segment became perfectly isoelectric. Figure 2 illustrates a typical tracing, showing progression from a definitely changed pattern back to normal. Similarly, partial recovery was considered to have occurred when the abnormal pattern

TABLE 2.—*Electrocardiographic Findings in Control Rats, Injured Untreated Rats, and Injured Rats given DCA*

Group	1	2		3	
Treatment	Control	Injured		Injured + DCA	
No. of animals	6	16		16	
No. with ECG changes:					
2nd & 3rd post-operative days					
definite	0	14	16	10	14
suggestive	0	2		4	
none	6			2	
4th post-op. day					
dead		2		0	
definite		4	15	3	8
suggestive		9		5	
none		1		8	
6th post-op. day					
definite		2		0	
suggestive		7	9	3	3
none		5		13	

was obviously regressing but the T segment was still below the isoelectric line.

Table 2 includes the electrocardiographic progress of the treated and untreated injured animals. It is apparent that the animals treated with DCA recovered a normal pattern more quickly than the untreated group. Thus, of the 14 animals in Group III (DCA-treated) which showed electrocardiographic changes, 6 had recovered by the fourth day (42.5 per cent). In contrast, of the 16 untreated animals (Group II) which showed electrocardiographic changes, only one (6.2 per cent) had recovered by the fourth day. By the sixth day, 11 of the 14 animals (78 per cent) in the treated group had completely recovered as judged by the electrocardiogram, while the remaining 3 had partially recovered. In contrast, at this time only 5 of the 16 untreated animals (31.2 per cent) had recovered, 7 showed partial recovery, and 2 were still grossly abnormal.

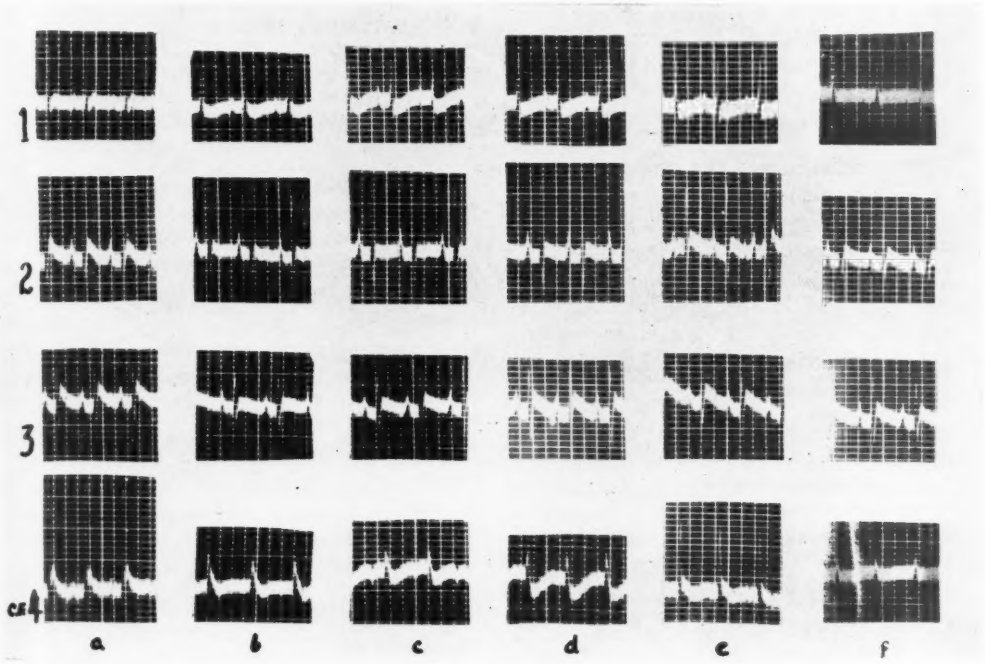

FIG. 2.—Recovery after injury. (a) Control. (b, c, d) Inversion of T wave in Leads I and IV on successive postoperative days. (e) Fourth postoperative day, T_1 segment still depressed. (f) Sixth postoperative day, T_1 segment now isoelectric.

DISCUSSION

As a working hypothesis, it was postulated that the release of potassium from a necrotic area of heart muscle might affect the electrical potentials developed in the surrounding zone. On this premise, the electrocardiogram in rats with a myocardial injury was studied in order to ascertain whether the administration of potassium or, conversely, its lowering, would alter the course of electrocardiographic events. Under the specified experimental conditions used here it was observed that added potassium exerted a deleterious effect on the electrocardiograph, while the administration of DCA, possibly acting through a lowered potassium, appeared beneficial. While these results support the original hypothesis, they do not, of course, preclude other explanations.

From the practical standpoint, these results should be considered in relation to myocardial infarction in man. Although the acute pro-

cedure used here for the production of cardiac injury does not bear any similarity to events in the human episode, presumably the potassium changes postulated might obtain regardless of how cardiac necrosis occurred. It seems to us, however, that extending these observations from the rat to man directly is not without hazard. These data regarding the beneficial effect of DCA on the electrocardiographic pattern of rats damaged by a myocardial burn are presented in the hope that the suggestive results obtained may receive amplification and the suggested hypothesis be confirmed or refuted.

Summary

1. Myocardial injury was produced in rats by searing a small area of the epicardial surface. The evolution of electrocardiographic changes was followed.

2. The administration of added potassium parenterally and in the drinking water increased the severity of electrocardiographic changes, while treatment with DCA had an apparently beneficial effect.

Acknowledgments

The authors wish to thank Dr. W. Alan Wright and Mr. W. E. Fielding of the Schering Corporation, who generously supplied the Cortate pellets used in this work, and Frank W. Horner Ltd. of Montreal who donated the electrocardiograph.

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Electrical Effects of Stimulating the Endocardial Surface of the Right Ventricle of the Dog

By ALBERT M. ATTYAH, M. D.

The endocardial surface of the right ventricle in four dogs was stimulated by a unipolar electrode introduced into the cavity of the right ventricle by means of a catheter. Electrical changes at a suprajacent point on the right wall were recorded by the V lead method of Wilson. In every experiment the induced QRS complexes were initiated by a positive electrical change.

THERE is considerable difference of opinion regarding the polarity of the initial electrical change recorded from a point on the thoracic wall when the endocardial surface of the subjacent ventricular wall is stimulated. Lewis and Rothschild[1, 2] reported that for the free wall of the right ventricle the initial change in potential, relative to a point transversely across the thorax is positive, whereas an initially negative deflection appears when the epicardial surface is stimulated. On the other hand, Nahum and Hoff[3, 4] report that both endocardial and epicardial stimulation produce the same effect, namely, an initially negative deflection at a suprajacent point on the thoracic wall. Of course the thorax, previously opened, had been closed, and the lungs inflated, when the stimuli were applied. Hoff's view is that the endocardial response may contribute to electrical changes, but that the sign of the electrical effect is the same, whether endocardium or epicardium is first stimulated.[5]

In a previous paper,[6] reasons were given for doubting the adequacy of the method employed. The results reported might have been due to an air pocket between the external pair of stimulating electrodes and the inflated lungs, to the use of too strong a stimulus, or to refractoriness of the endocardial surface at the moment the stimulus was applied in the rapidly beating heart. The usual form of the T wave, at least in the human electrocardiogram, suggests slower electrical recovery of the endocardial than of the epicardial muscle surface, and this indicates that the inner surface has a longer refractory period.

For these reasons, we decided to stimulate the endocardial surface of the right ventricle by means of a wire passed through a catheter, the end of which, after the catheter was passed through the jugular vein, was in contact with the inner surface of the free wall of the right ventricle. The tip of the wire was rounded to prevent injury by attaching a small globule of soldering metal to it. The stimulus was unipolar, being delivered from the secondary of an inductorium. The indifferent electrode was a metal plate placed at a distance on the dog's body. The stimulus strength was adjusted so that responses were obtained on the break, but not on the make. This precluded too strong stimulation. Before stimulating, the right vagus was faradized, this being continued for several seconds while the stimuli were being applied to the ventricle. Arresting the heart by vagus stimulation accomplished two things: it assured complete recovery of the muscle from refractoriness before the shock was applied, and it permitted the tip of the catheter and wire to come to rest in contact with ventricular wall. Fluoroscopic examination was used to place the catheter, and a roentgenogram was taken to show the positions of stimulating and recording electrodes. Furthermore, the location of the tip of the catheter was confirmed at autopsy. No effort was made to stimulate the epicardial surface, since all observers agree that with such stimulation, the initial electrical

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change is negative. For recording, a string galvanometer was connected to the precordial electrode and Wilson's central terminal. The precordial electrode was placed on the right precordium suprajacent to the part of the right wall which was stimulated. Positivity at the electrode yielded an upright deflection. Four dogs were used.

described in the legends. In two of the four dogs, ectopic beats appeared, probably as a result of mechanical stimulation. Although the locus of stimulation cannot be determined with certainty, it was presumably the same as the locus of electrical stimulation. Associated with these responses there is, of course, no electrical signal of stimulation. Their form is identical

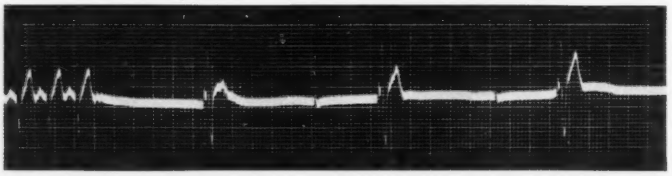

FIG. 1. V lead from right precordium. The first three complexes are the regular sinus rhythm. The vagus is stimulated with cardiac arrest. A break shock is applied, at the time of the white dot to the left of the S wave of the fourth QRS complex. This is followed by the upward portion of the diphasic artefact due to the shock. The R wave, with a white dot at its apex, follows. At the position of the next dot, the diphasic artefact due to the subthreshold make shock is seen, and this is followed by two other break shocks, with response, and an intervening make, without response. Time, 0.04 and 0.20 second.

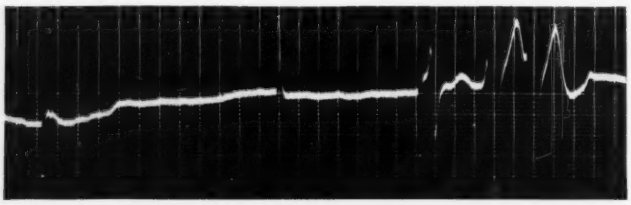

FIG. 2. V lead from right precordium. More rapid film, taken during vagus stimulation. Time intervals, 0.10 sec. At left, the diphasic artefact due to an ineffective break shock. Just left of center, make shock artefact. This is followed by a break and the RS form of QRS complex. Two premature beats, probably mechanically induced, follow the QRS complex being of RS form in each. The R wave of the second premature beat is reduced in apparent amplitude because it occurs on the rapidly descending limb of a T wave.

RESULTS

The results were the same in all four of the animals. Among hundreds of responses, none began with a negative deflection. A relatively narrow R wave (positive) appears immediately after the artefact signalling stimulation by the break shock, and this is followed by a much wider S wave (negative). This is the same as the result reported with endocardial stimulation by Lewis and Rothschild, except the arrangement of the electrodes in their experiments caused initial positivity to produce a downward deflection. One of their records is shown in Lewis' book. Samples of results from two dogs are shown in figures 1 and 2, and are (in both animals) with the form obtained by electrical stimulation.

DISCUSSION

These results are in agreement with those to be expected on the basis both of electrical theory and of findings with ventricular strips or whole turtle ventricles immersed in a volume conductor.[7] When the inner surface of the right ventricle is activated, the wave of excitation begins to spread outward through the wall. A positive field is in advance of the wave, whereas the ventricular cavity would be rendered negative. This wave, approaching the precordial electrode, makes it positive, relative to the

central terminal. As soon as the entire thickness of the right wall is activated over an area of critical size, the wave of excitation, now retreating from the electrode through the septum and left ventricle, renders the electrode negative and an S wave is produced. Since the right wall is thin, the R wave is narrow in comparison with the S wave.

Conclusion

Contrary to another report, but in agreement with Lewis and Rothschild, it was found that electrical stimulation of the endocardial muscle surface of the free wall of the right ventricle produced initial positivity of a suprajacent galvanometer electrode in all trials in the hearts of four dogs.

Acknowledgments

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Arrhythmias during Intracardiac Catheterization

By J. Michel, M.D., A. D. Johnson, M.D., W. C. Bridges, M.D., J. H. Lehmann, M.D., F. Gray, M.S., L. Field, A.B., and D. M. Green, M.D.

This paper summarizes the incidence of various arrhythmias in an unselected series of cardiac catheterizations and presents evidence for their reflex origin in some instances. The hazards are discussed and comments made about prophylaxis and treatment.

THE PATIENT who undergoes cardiac catheterization may develop an arrhythmia. It would be useful to know who is most susceptible, how hazardous the arrhythmia may be and what can be done about it.

Cournand[1] mentioned premature contractions and runs of ventricular tachycardia as the most important complication in the procedure. Two cases were quoted in which death may have been the result of ectopic rhythms. Dexter[2] reported irregularities of the heart in 27 out of 42 cases; 14 had symptoms referable to the arrhythmia. Bloomfield[3] noticed many ventricular premature systoles, while Levine[4] described seven cases with disorder of the heart beat of auricular origin with the tip of the intracardiac electrode in the right auricle. He found that a high percentage of subjects developed arrhythmias when the tip was in the right ventricle. Most reports infer that the great majority of irregularities are of ventricular origin, induced when the catheter, especially its tip, is in the vicinity of the interventricular septum.

The present study details the type and incidence of disorders in the cardiac mechanism noted in a consecutive series of cardiac catheterizations performed during a one-year period. The influence of age, sex, diagnosis, pulse rate and blood pressure has been analyzed.

Methods and Materials

One hundred and thirty-three patients were subjected to cardiac catheterization. Sixty per cent were men. The ages ranged from 7 months to 75 years. The diagnostic grouping is detailed in table 1.

A general anesthetic was administered in five cases. Local procaine infiltration was used in the remainder following premedication with sodium phenobarbital in a dose of 3 mg. per kilogram. A standard cardiac catheter was introduced into the heart in most instances by way of the antecubital vein. A direct-writing electrocardiograph was observed continuously during the procedure. The location of the catheter tip was determined fluoroscopically. Its position was also checked by measurements of pressure and blood oxygen saturation. In some questionable cases, roentgenograms were taken.

In evaluating the results of these studies, variability in any factor has been expressed as the standard deviation. Significance of differences between mean values was determined by calculating the ratio of the difference between means to the standard error of the difference.

Results

Incidence of Arrhythmias in Relation to Location of Catheter Tip

Arrhythmias were noted in 37 per cent of all patients catheterized (table 2). The incidence of arrhythmias was 19 per cent with the catheter tip in the right atrium, 20 per cent in the right ventricle and 19 per cent in the pulmonary arterial tree. The arrhythmias associated with the presence of the tip in the right atrium included four instances of sinus bradycardia, three of premature auricular systoles, two of paroxysmal auricular tachycardia, twenty of premature ventricular systoles, five of paroxysmal ventricular tachycardia, and one intraventricular block. The presence of the catheter tip in the right ventricle coincided with twelve cases of premature ventricular systoles, six of paroxysmal ventricular tachycardia and one of bigeminal rhythm. With the tip in the pulmo-

These studies were supported by a grant from G. D. Searle & Co., Chicago, Illinois.

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nary arterial tree there occurred three instances of premature ventricular systoles, one of bigeminal rhythm, three of paroxysmal ventricular tachycardia and one of intraventricular block.

In many instances, the point of origin of ectopic impulses coincided with the position of the catheter tip at the time of origin. In others, the initiation of impulses appeared compatible with direct stimulation by some portion of the catheter proximal to the tip. In a considerable number of cases, however, intra-auricular locations of the catheter tip were associated with a variety of extra-auricular rhythms. It appeared difficult to explain the mechanism of impulse origin in these instances except on a basis of reflex excitation consequent upon stimulation of some portion of the endocardial or endothelial surface other than the point of impulse formation.

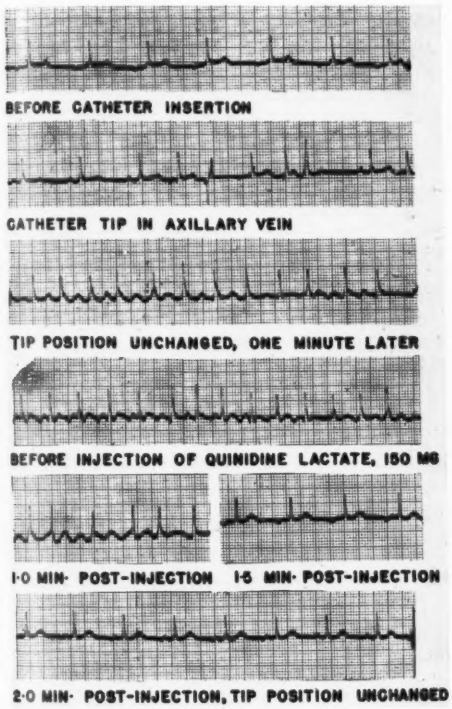
BEFORE CATHETER INSERTION
CATHETER TIP IN AXILLARY VEIN
TIP POSITION UNCHANGED, ONE MINUTE LATER
BEFORE INJECTION OF QUINIDINE LACTATE, 150 MG
1·0 MIN· POST-INJECTION
1·5 MIN· POST-INJECTION
2·0 MIN· POST-INJECTION, TIP POSITION UNCHANGED

FIG. 1.—Paroxysmal fibrillation following insertion of catheter into vein. (All sequences taken with Lead II.)

In support of the latter hypothesis, serious arrhythmias followed insertion of the catheter in three instances before the tip had been advanced into the superior vena cava. In one subject, a young man suffering from an old traumatic arteriovenous aneurysm, the arrhythmia took the form of paroxysmal auricular fibrillation (fig. 1). The second subject was a young woman with mild rheumatic mitral disease and a severe cardiac neurosis. Alternating runs of paroxysmal auricular and ventricular tachycardia developed before the catheter had been advanced past the axilla (fig. 2). The third subject was a cyanotic baby 7 months of age, in whom a series of varied arrhythmias was initiated immediately following introduction of the catheter into the venous tree (fig. 3). In two other instances, severe sinus bradycardia

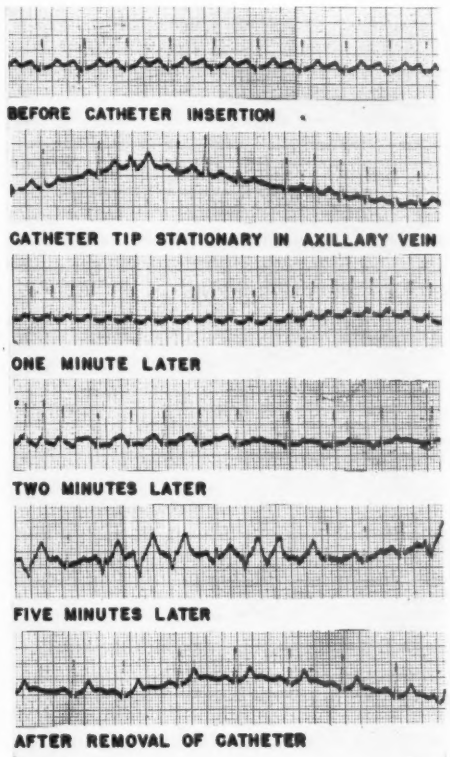

FIG. 2.—Paroxysmal tachycardia following insertion of catheter into vein. (All sequences taken with Lead II.)

TABLE 1.—*Diagnostic Grouping of 133 Patients on Whom Venocardiac Catheterizations Were Performed*

Diagnosis	Number in Subgroup	Number Who Developed Arrhythmias
Hypertensive cardiovascular disease	68	17
Congenital heart disease	23	13
Coronary heart disease	14	8
Toxemia of pregnancy	5	0
Rheumatic heart disease	5	3
Cor pulmonale	3	1
Noncardiac diseases	15	7
Total	133	49

TABLE 2.—*Incidence of Arrhythmias in 133 Cases of Venocardiac Catheterization*

	Number of Cases	Percent of Cases
Group which developed arrhythmias	49	37
Group which did not develop arrhythmias	84	63

Type of Arrhythmia	Number of Instances	Percentage Incidence
Premature ventricular systoles	35	55
Paroxysmal ventricular tachycardia	14	22
Sinus bradycardia	6	9
Premature auricular systoles	3	4
Paroxysmal auricular tachycardia	2	3
Bigeminal rhythm	2	3
Intraventricular block	2	3

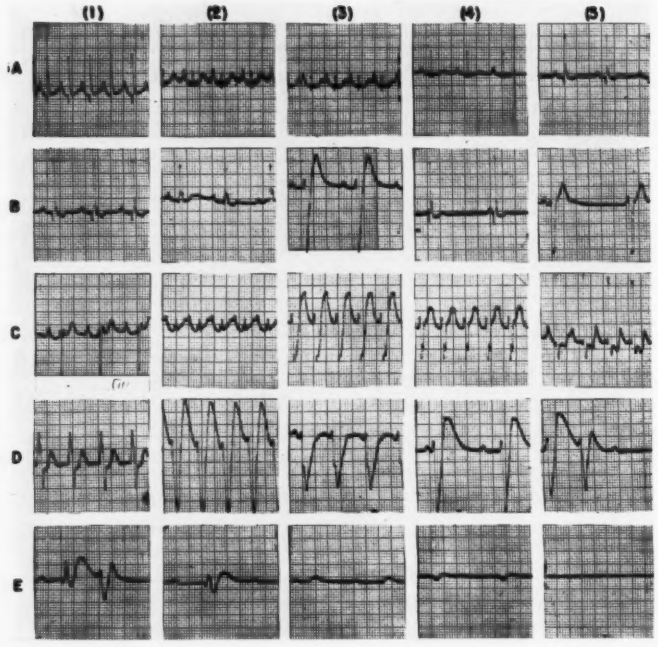

FIG. 3.—Arrhythmias initiated by insertion of catheter into vein. (All sequences taken with Lead III.)

A (1) illustrates pre-insertion pattern. (2) was taken immediately following catheter insertion. The remainder of the tracings represent return to pre-insertion values when the catheter insertion was halted.

B The sequences follow a second attempt at movement of the catheter in the direction of the vena cava.

C–E were taken after the catheter had been removed from the vein.

with vasovagal syncope appeared to have been initiated by the withdrawal of the catheter after uneventful diagnostic studies (fig. 4).

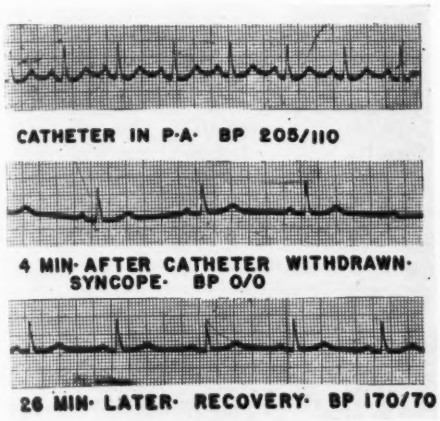

FIG. 4.—Sinus bradycardia following withdrawal of the catheter and completion of diagnostic studies (All sequences taken with Lead II.)

TABLE 3.—*Incidence of Pre-existing Electrocardiographic Abnormalities in 133 Patients Subjected to Venocardiac Catheterization*

Pattern*	Number in Group	Percent in Group
Normal	48	36
Borderline or abnormal	85	64

Type of Abnormality*	Number	Number Who Developed Subsequent Arrhythmias
Left heart strain	18	5
Low voltage	18	7
Premature ventricular systoles	11	9
Intraventricular block	11	3
Premature auricular systoles	6	3
Right heart strain	5	3
Auricular fibrillation	4	2
Sinus arrhythmia	2	1
Chronic coronary insufficiency	2	3

* Terminology in accordance with that proposed by Katz.[5]

These instances indicate that the procedure, rather than the presence of the catheter or the tip location, is the factor primarily responsible for the development of certain of the arrhythmias associated with catheterization.

Incidence in Relation to Diagnostic Classification

The incidence of arrhythmias was greatest in patients with congenital heart disease (table 1). The percentage occurrence in this class was approximately twice as high as that in the remainder of the group, a difference which proved significant ($t = 3.10$).

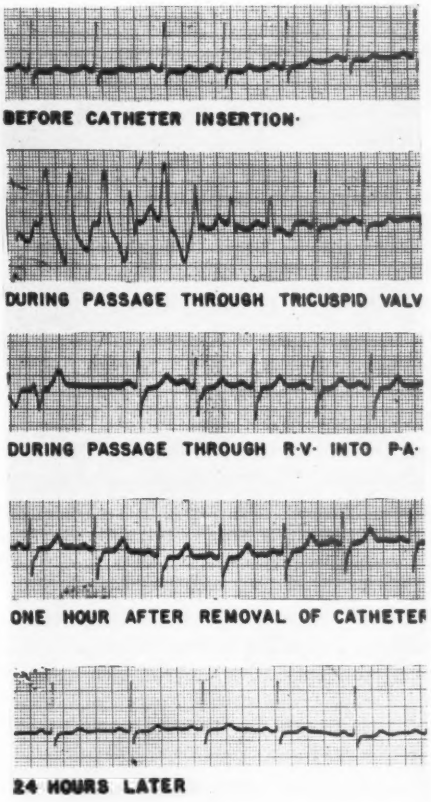
BEFORE CATHETER INSERTION·
DURING PASSAGE THROUGH TRICUSPID VALV
DURING PASSAGE THROUGH R·V· INTO P·A·
ONE HOUR AFTER REMOVAL OF CATHETER
24 HOURS LATER

FIG. 5.—Intraventricular block initiated by passage of catheter through the right ventricle, with persistence for hours after the catheter had been withdrawn. (All sequences taken with Lead III.)

Significant correlations were not demonstrated for any other diagnostic classification.

Age, sex and pre-existing pulse rate and blood pressure levels bore no statistically significant relation to the incidence of arrhythmias. An

apparent correlation with age was due to the greater number of patients with congenital heart disease in the younger age group.

Relation to Precatheterization Electrocardiograms

Control electrocardiograms were taken on all subjects to determine the presence of pre-existing abnormalities (table 3). Only 27 per cent of those with normal patterns developed arrhythmias; in contrast, the incidence among patients with prior abnormalities was 44 per cent. This difference proved significant ($t = 2.07$). No one type of electrocardiographic abnormality was present with sufficient frequency to permit correlation with subsequent development of arrhythmias.

Treatment of Arrhythmias

In the vast majority of cases, arrhythmias ceased when the catheter was moved to a different location. In six subjects removal of the catheter was required. In four of these, the arrhythmias subsided at once. In the fifth case, a bundle branch block persisted for several hours, then disappeared (fig. 5). Extensive studies failed to demonstrate any associated symptoms or signs. The sixth subject was the cyanotic baby previously mentioned. This child subsequently proved to have been suffering from a complete transposition of the aorta and pulmonary arteries associated with a patent foramen ovale and a small, high ventricular septal defect. Induction of Pentothal anesthesia preparatory to catherization was marked by transient arrest of voluntary breathing overcome after a period of artificial respiration. The arrhythmias which followed insertion of the catheter persisted after its withdrawal. A normal rhythm was never re-established and a second period of respiratory failure led to a fatal outcome two hours later.

One other child with congenital disease developed temporary respiratory arrest during induction of Pentothal anesthesia. The procedure was terminated. This subject and two others were catheterized subsequently under Avertin anesthesia with no untoward effects.

The one instance of paroxysmal auricular fibrillation was controlled by intravenous injection of quinidine lactate. Vasovagal syncope responded in every case to ephedrine. The prophylactic injection of 25 mg. of ephedrine prior to removal of the catheter eliminated the occurrence of this arrhythmia following the procedure.

Summary

Thirty-seven per cent of 133 patients developed arrhythmias during venocardiac catheterization. The incidence was significantly higher in patients with congenital heart disease and in patients with pre-existing electrocardiographic abnormalities. Significant relations were not established with age, sex, heart rate, or blood pressure.

All arrhythmias were transitory with one exception. In that instance, anesthetic depression of the respiratory center in combination with a catheter-induced arrhythmia appeared to have contributed directly to a fatal outcome. The experience with anesthetic agents indicates that one episode of respiratory arrest following Pentothal anesthesia in a cyanotic child is a clear-cut indication not to proceed with the cardiac catheterization.

A percentage of arrhythmias appeared inexplicable on the basis of direct stimulation of the site of impulse formation. The hypothesis is advanced that such arrhythmias may have resulted from reflex activity which excited normal or ectopic foci of impulse formation.

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Ventricular Tachycardia during Cardiac Catheterization of Patient with Wolff-Parkinson-White Syndrome

Report of a Case Showing Effects of Atropine Sulfate

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MARION E. MCDOWELL, M.D., AND RAYMOND PEARSON, M.D.

Cardiac catheterization of a patient with probable Wolff-Parkinson-White syndrome was attempted to clarify the possibility of coexistent congenital heart disease. Introduction of the catheter into the heart induced a multifocal ventricular tachycardia which endangered the life of the patient. After quinidine and other drugs had failed to control the arrhythmia that persisted for nine hours, a prompt and gratifying conversion to supraventricular tachycardia, and subsequently to sinus rhythm, followed the intravenous administration of atropine sulfate.

THE Wolff-Parkinson-White syndrome consists of an abnormally short P-R interval, usually prolonged duration of QRS complexes, and history of repeated episodes of paroxysmal tachycardia.[1] Variations of QRS complex have been observed during tachycardia, following exercise or atropine sulfate,[1] or even while patients were at rest.[2] The paroxysmal tachycardias have been generally supraventricular, especially auricular, occasionally auricular fibrillation,[1] and rarely paroxysmal ventricular tachycardia.[3–8] Although the Wolff-Parkinson-White syndrome is usually unassociated with organic heart disease, rheumatic disease has been observed not infrequently.[13] Sudden death of patients with this syndrome has warranted a guarded prognosis.[14]

Short paroxysms of ventricular tachycardia are known to occur occasionally during cardiac catheterization and to stop promptly following partial withdrawal of the catheter tip.[9] Two cases of Wolff-Parkinson-White syndrome, subjected to cardiac catheterization, have been reported by Ferrer and associates.[10] Each exhibited paroxysms of supraventricular tachycardia without apparent hazard to their welfare. The following case is reported because it presents two features of interest: the occurrence of repeated paroxysms of ventricular tachycardia with multifocal characteristics in a patient with cardiac enlargement and Wolff-Parkinson-White syndrome, and the striking benefit of intravenous atropine sulfate in the control of this arrhythmia when quinidine and other medications had failed.

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CASE REPORT

A 26 year old Italian man has had repeated attacks of paroxysmal tachycardia since 1929. He has had slight cyanosis, clubbing, and splitting of the first sound with a harsh systolic murmur at the apex transmitted to axilla. He also had low grade fever for a prolonged period of time during childhood.

Since then he has had repeated attacks of paroxysmal tachycardia, three or four times a year. Often the attacks could be controlled by ocular pressure. A chest film showed cardiac enlargement, and fluoroscopy revealed slight prominence of the left auricle, and no hilar dance.

An electrocardiogram taken in September, 1949 (Fig. 1, left) showed moderate left axis deviation, sinus rhythm, short P-R interval of 0.10 second, and deformed and slurred QRS complex indicative of the Wolff-Parkinson-White characteristics resembling type 1 of Burch and Kimball.[2] The Q-T interval was 0.44 second, and the K ($Q\text{-}T_c$), 0.459. The R waves were prominent in Leads aV_L and V_5. Stethocardiograms revealed a systolic murmur at the apex, presystolic sound at the aortic area following the P wave of the electrocardiogram and an early diastolic de-

crescendo murmur along the left sternal border in the third and fourth intercostal spaces. The arterial blood oxygen saturation was 84 per cent with pO_2 49 mm. Hg; the hemoglobin was 20.3 Gm. per 100 cubic centimeters.

Cardiac catheterization was performed with a double catheter (sampling tube and intracardiac electrode combined) inserted into the right arm vein. Under fluoroscopic control, the catheter was readily passed into right atrium to the region of the tricuspid valve. Immediately the patient complained of palpitations and tachycardia. Neither ocular pressure nor carotid sinus pressure were effective. He rapidly became apprehensive, restless, and ashen gray with a cyanotic tint, and perspired profusely; the blood pressure was unobtainable. The peripheral pulse at the wrist was irregular, faint, and about 50 to 70 per minute. A very rapid irregular rate was observed at the apex of the heart. The legs were raised to aid venous return and oxygen therapy was instituted. Electrocardiograms revealed multifocal ventricular tachycardia with a rate of 220 to 250 per minute (Fig. 1, right B). Quinidine sulfate, 0.4 Gm., given by mouth, and followed in half an hour by 0.6 Gm. quinine dihydrochloride intravenously, was without any effect. Short intervals of bizarre low-voltage complexes suggestive of incipient ventricular fibrillation were observed frequently during almost continuous recording of a chest lead electrocardiogram on a direct-writing instrument. The patient never lost consciousness although he showed signs of cerebral anoxia. Nine hours later, after futile efforts using morphine sulfate (0.016 Gm.), magnesium sulfate (1.0 Gm.), and a total dose of 2.4 Gm. of quinidine sulfate (plus 0.6 Gm. quinine dihydrochloride parenterally), intravenous 1.0 per cent procaine, and niacinamide, there was no significant change (Fig. 2, upper). Then 1.2 mg. of atropine sulfate was administered intravenously and promptly the bizarre ventricular tachycardia converted to a supraventricular tachycardia which superficially resembled auricular flutter with a 2:1 block and ventricular rate of 146 per minute which lasted six hours (Fig. 2, lower). (It may have been a nodal tachycardia with retrograde depolarization of the auricles.) Gallop rhythm and snapping of the first heart sound were noted. Finally the tachycardia reverted to a sinus rhythm, with a rate of about 86 per minute, and the color, heart rate, blood pressure and heart sounds were restored to normal. There were no signs of congestive heart failure. He was kept on a maintenance dose of quinidine sulfate, 0.4 Gm. every six hours, for the next few days without any recurrence of tachycardia. Electrocardiographic and pneumocardiographic study after restoration of normal sinus rhythm failed to show any residual effects of the tachycardia. The patient recovered strength, felt well, and was discharged five days later.*

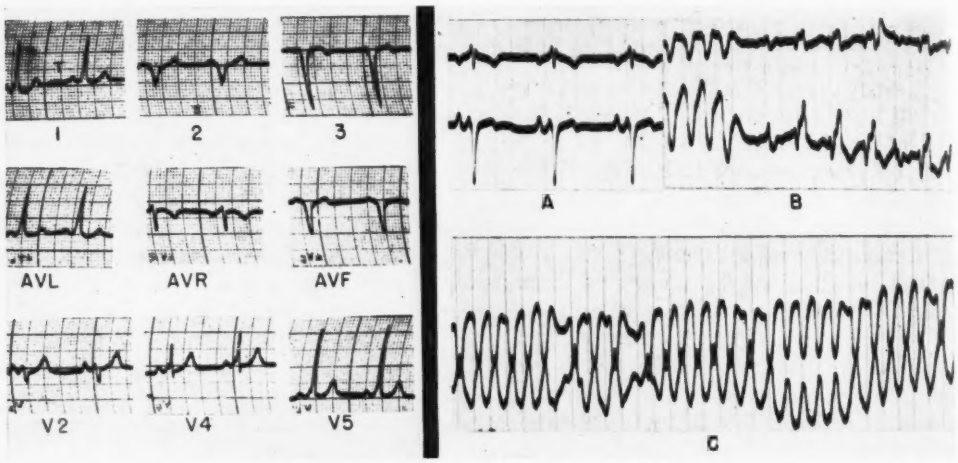

FIG. 1.—*Left:* Current electrocardiographic findings during Wolff-Parkinson-White mechanism with normal rate. Note the slurred upstroke of QRS in Leads I and a V_L, notched QRS in Leads III, V_2, V_4 and V_5 with short P-R interval. *Right: A.* Control tracing when catheter tip was in superior vena cava (upper tracing shows intracardiac lead, lower tracing V_1 lead). *B, C.* Paroxysmal ventricular tachycardia arising from various foci.

* An exercise tolerance test[11] performed eighteen days after the paroxysmal ventricular tachycardia showed a conspicuous reduction in the physical fitness index from 16 to 10.6 due to tachycardia.[12] Subjectively the patient did not tolerate the exertion as well as before but denied any specific symptoms.

The history is confusing in determining the cause of the cardiac enlargement. The laboratory data are compatible with rheumatic mitral valvulitis, auricular hypertrophy, and pulmonary insufficiency. Presumably the hypoxemia indicates right-to-left shunting of blood from an unrecognized auricular septal defect, or diffuse vascular anastomoses of the lungs. Unfortunately the ventricular tachycardia precluded a definitive diagnosis. The persistent arrhythmia did not respond to reflex vagal stimulation. Significant quantities of quinidine, niacinamide, magnesium sulfate, morphine sulfate,* as well as procaine hydrochloride (up to 350 mg. intravenously) failed to revert the arrhythmia. However the intravenous adminis-

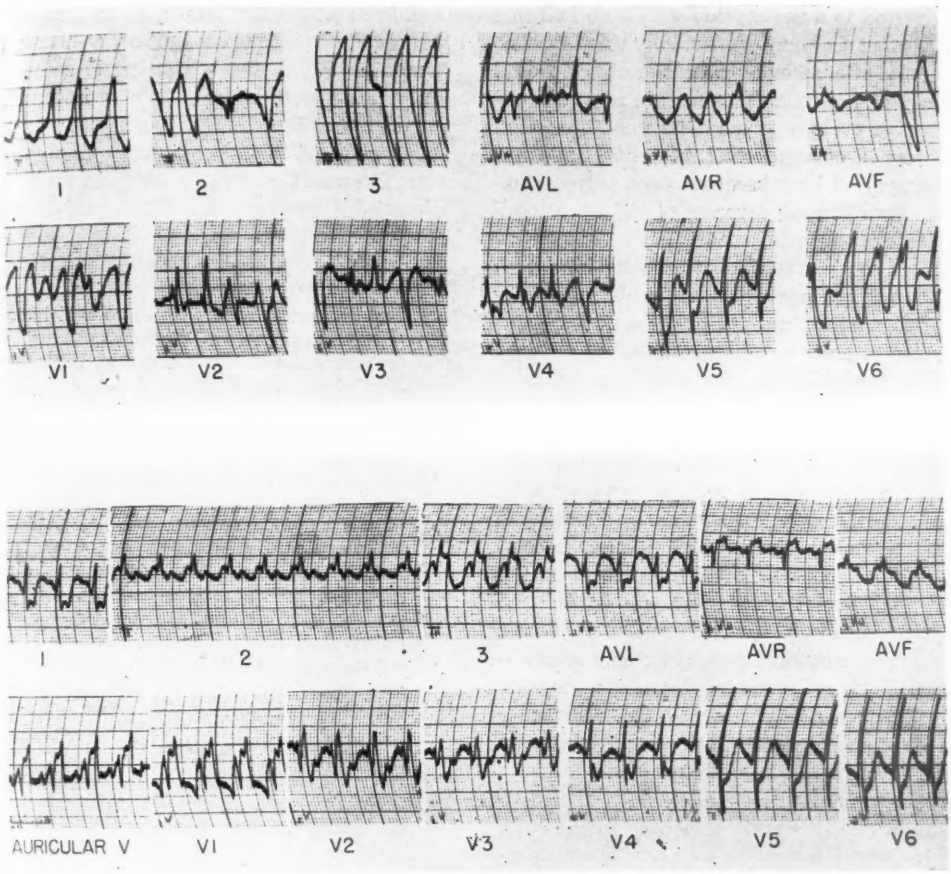

FIG. 2.—*Above:* Electrocardiograms obtained after nine hours of sustained paroxysms of ventricular tachycardia with associated circulatory collapse. Note occasional QRS complex of supraventricular characteristics. *Below:* Electrocardiograms obtained immediately after intravenous administration of 1.2 mg. of atropine sulfate. Superficial appearance in Lead II resembles auricular flutter with 2:1 block, but this may well be nodal tachycardia with re-entrant depolarization of auricles. A conspicuous injury current, indicated by S-T segment changes, with high voltage T waves in Leads I, V_4, V_5, and V_6 are apparent. Approximately six hours later this spontaneously changed to sinus rhythm with a normal rate, and showed neither RS-T segment nor T-wave alterations; these tracings not reproduced since they appear the same as those in figure 1.

* Sabathie[15] found that morphine sulfate, 0.01 to 0.04 Gm. intravenously, was effective in controlling paroxysmal ventricular tachycardia in 9 out of 10 patients.

tration of 1.2 mg. of atropine sulfate was promptly followed by a conversion to supraventricular tachycardia, either auricular flutter with 2:1 block, or nodal tachycardia with reentrant auricular depolarization. This in turn converted to sinus rhythm with a normal rate in another six hours. Fortunately there were no sequelae after recovery indicative of myocardial injury or ischemia. This feature has been observed in other reported cases when the initial impression of myocardial infarction could not be supported by subsequent events. Nevertheless, the alarming severity of the circulatory collapse observed in this patient stood in marked contrast to the not infrequent episodes of fleeting paroxysms of ventricular tachycardia recorded during manipulation of the intracardiac catheter in other patients.

The mechanism of the beneficial action of atropine sulfate in converting a ventricular to a supraventricular tachycardia is largely speculative. It is known that atropine may prevent the occurrence of ventricular tachycardia during cyclopropane anesthesia or epinephrine induced tachycardia in dogs.[16] Wilburne and co-workers believed that atropine acts on the "acetylcholine-cholinesterase" mechanism to prevent reflex vagal-induced premature systoles, paroxysmal ventricular tachycardia, and fibrillation. Further experimental studies in dogs by Lenel and associates[17] indicated that ventricular tachycardia is induced by hyperexcitability of the idioventricular pacemakers in the presence of epinephrine, or by stretching of the myocardium due to a sudden increase in pressure, or by vagal inhibition of the higher pacemakers. Bilateral vagotomy always stopped the paroxysm, and neither epinephrine nor vagal stimulation alone was capable of inducing a paroxysm in the vagotomized animal. Furthermore, ventricular tachycardia can be inhibited by pentobarbital anesthesia, dibenamine, and to some extent morphine.[18]

Summary

An unusual case of multifocal paroxysmal ventricular tachycardia occurring during cardiac catheterization in a patient with cardiac enlargement and probable Wolff-Parkinson-White syndrome is reported. The etiology of the heart disease was not established, but features indicative of rheumatic valvulitis and congenital septal defect could not be excluded. The tachycardia was accompanied by profound circulatory collapse and did not respond to quinidine sulfate by mouth, or to quinine dihydrochloride intravenously. Intravenous atropine sulfate (0.0012 Gm.) promptly converted the ventricular tachycardia to a supraventricular tachycardia resembling auricular flutter, which changed to sinus rhythm with a normal rate. The possible actions of atropine are briefly discussed.

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Electrokymographic Studies of the Normal Cardiac Cycle

By HENRY MEDNICK, M.D., JOHN B. SCHWEDEL, M.D., AND PHILIP SAMET, M.D.

Normal subjects were studied by employing two electrokymograms simultaneously. By comparing the sequence of events in the carotid pulse, auricle and ventricle, measurements were made of the phases of the cardiac cycle. The normal electrokymogram is discussed and illustrated. Simultaneous electrokymography of the right- and left-sided chambers and vessels of the heart provides a simple method for comparing synchronicity of events in normal and pathologic states. Data obtained in normal subjects is presented.

CARDIOLOGISTS and physiologists have long sought to develop clinically feasible methods of recording and studying the mechanical and electrical phases of the cardiac cycle in intact man. No one will deny that success has crowned efforts to record the electrical potentials developed in the heart. Recording of peripheral arterial and venous pulsations and heart sounds has also become routine procedure. One of the remaining hurdles has been the recording of the motion of the heart borders. Among the methods used for the latter purpose the roentgenokymogram is the best known. Applications of this method proved to be limited in scope.[1–7] In the past two decades various attempts have been made to record the heart border, as seen fluoroscopically, with the aid of a photoelectric tube.[8–11] The most successful device currently in use was developed by Henny and Boone.[12, 13] This consists of a multiplier photoelectric tube with a fluorescent screen activated by the roentgen rays which have passed through the subject being studied. Filters are employed to remove interference created by the roentgen tube. Henny and Boone employed a simultaneous recording of the carotid pulse as a timing device. Luisada and co-workers[14,15] have used the heart sounds, while Anderson[16] has resorted to the electrocardiogram.

Electrokymography has proved to be of great value. Accurate recording of the motions of the cardiac contour is now possible and studies of the various phases of the cardiac cycle, especially the isometric relaxation phase, have been undertaken.[17–19] Studies of asynchronous contractions of the auricles and ventricles in normal individuals and in those with bundle branch block have been reported.[20, 21] Confirmation of assumptions made in the course of these investigations has been achieved by correlation of electrokymographic curves with intra-auricular and intraventricular pressure curves.[22] The possibility of determining stroke volume and cardiac output with this technic is under investigation.[23, 24] A recent review of electrokymography has been published.[25]

We have been interested in correlating the electrical and mechanical events of the cardiac cycle and in measurement of the phases of the cardiac cycle in heart disease. With this view in mind we have undertaken a study of a group of normal individuals. As a further aid in our investigation we have recently been employing two electrokymographs with simultaneous recording of either the carotid pulse or an electrocardiogram. This has been made possible by the use of a direct writing tri-beam Technicon. We now feel that a direct writing recorder is a necessity because it enables immediate visualization allowing for adjustment of the photoelectric cell if unsatisfactory curves are obtained.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Technic

Initially a Cambridge Simpli-Trol* electrocardiograph was used; this permitted simultaneous recording of an electrokymogram, carotid pulse, and heart sounds. Because of frequent superimposition of the curves and because immediate visualization of the recording was not possible we found this instrument limited in application. With the acquisition of a direct writing Technicon† our work was greatly facilitated. This instrument has devices for eliminating 60 cycle interference, and for critical damping of each stylus. There is a 100 per cent frequency response to almost 50 cycles per second.

The electrokymograms were all taken with the subject in the sitting position and the photoelectric pickup tube between him and the fluoroscopic screen. Fluoroscopy was done at 70 kilovolts and 4 milliamperes. Because of the sharper end points obtained the paper speed was 25 mm. per sec. rather than 50 mm. per sec. Tracings were taken in the posteroanterior and in both oblique positions thus allowing for complete exploration of the cardiac contour. Two Cambridge electrokymogram pickup units were employed. The carotid pulse tracing was obtained by placing a pulse-microphone over the vessel, the current of which was fed through one channel of the recording apparatus.

The results will be presented in three groups. In the first group the photographic recorder was used. In the second group a single electrokymogram was recorded with the direct writing machine and in the third group two electrokymograms were recorded simultaneously with this machine.

Data

The subjects used in the studies were patients on the medical and surgical services of this hospital in whom the presence of cardiac disease was ruled out by history, physical examination, fluoroscopy and electrocardiography. Electrokymograms were taken with the patient in the sitting position. During the recording period the patient was instructed to stop breathing in mid-inspiration and to avoid straining.

Group 1. Seventeen subjects were studied with a single electrokymogram with simultaneous recordings of the heart sounds and carotid pulse waves. In the posteroanterior position tracings of the left ventricle, left auricular appendage, pulmonary artery, ascending aorta and right auricle were made. In the left oblique position tracings of the left ventricle, right ventricle, ascending aorta and left auricle were taken. Whenever the quality of the tracings permitted, measurements of the various phases of the cardiac cycle were taken (see table 1). No fewer than four complexes were measured

Table 1.—*Measurements Obtained from 53 Subjects*

	Total Cases—All Methods			
	No. cases	Range		Average
Carotid				
Isometric contraction	52	.02	.05	.035
Total ejection	52	.16	.32	.229
Left Ventricle				
Isometric contraction	32	.03	.06	.041
Total ejection	31	.16	.26	.215
Isometric relaxation	47	.07	.14	.116
Right Ventricle				
Isometric contraction	5	.03	.07	.052
Ejection	2	.16	.18	.170
Isometric relaxation	8	.10	.13	.111
Ejection—Right Ventricle to Left Ventricle	5	.00	+.02	+.008
Pulmonary Artery and Aorta				
Ejection—Ascending Aorta to Carotid Ejection	41	.00	.04	.017
Ejection—Pulmonary Artery to Carotid Ejection	41	−.02	.05	.019
Pulmonary Artery to Aorta via Carotid Ejection	35	−.02	+.03	+.007
Pulmonary Artery to Aorta—Direct Measurement	21	−.02	+.03	+.008
Auricles				
A Wave—Right to Left	5	.00	+.06	+.018
C Wave—Right to Left	12	−.04	+.04	+.012
V Wave—Right to Left	14	−.04	+.04	+.025
Incisura (carotid) to V Wave Left	37	.05	.14	.101
Incisura (carotid) to V Wave Right	29	.00	.14	.066
Electrocardiogram				
PR Interval	35	.10	.17	.138
QRS Interval	36	.05	.09	.070
QRS to Carotid Ejection	35	.10	.16	.136
P Wave to A Wave Left	15	.10	.18	.132
P Wave to A Wave Right	13	.09	.18	.121

+ Indicates that right is ahead.

* The Cambridge Instrument Company, Inc., Ossining, New York.

† Technicon Cardiograph Co., New York, New York.

in each tracing and when a chamber was recorded in several views the average of all views was determined. The onset of systolic ejection in the pulmonary artery and in the ascending aorta was compared by using the onset of carotid ejection as a reference point. Similarly the sequence of opening of the tricuspid and mitral valves was measured by using the carotid incisura as a reference point. The beginning of the first heart sound was useful in identifying the onset of the isometric contraction curve of the left ventricle, and the carotid incisura (after a correction was made for a delay of .03 seconds) was useful in indicating the onset of the isometric relaxation curve of the left ventricle.

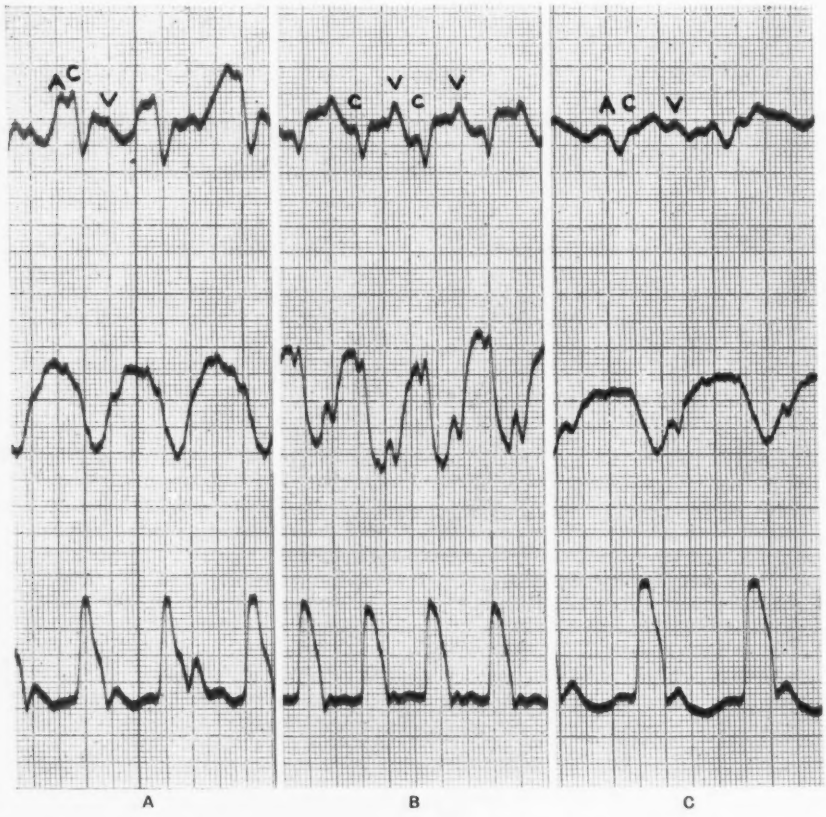

FIG. 1. Simultaneous electrokymograms of the left auricle, left ventricle, and carotid pulse tracing (top to bottom). The variations in the shapes of the curves is apparent, but the time relationships are constant. The peak of the "C" wave of the auricle is simultaneous with the downstroke of ejection in the ventricle and the upstroke of carotid ejection. The closing of the aortic valve is in indicated by the carotid incisura and the upstroke of isometric relaxation of the ventricle. The opening of the mitral valve is indicated by the auricular V wave and corresponds to the end of the isometric relaxation curve indicated by a short downstroke on the ventricular tracing. Auricular contraction inscribes the downstroke of the A wave.

Group 2. Twelve additional subjects were studied in the same fashion as group 1 with the following changes: A three channel direct writing recording machine was used; the heart sound tracing was replaced by a simultaneous electrocardiogram (usually Lead II); measurements of the onset of the Q wave of the electrocardiogram to carotid ejection and of the

onset of the P wave to the A waves of the electrokymogram were made.

Group 3. With the acquisition of a second electrokymogram our technic was altered so that simultaneous tracings of two heart borders or the two great vessels could be obtained. auricular appendage was always obtained even when this chamber was not apparent to the fluoroscopist. Simultaneous tracings of the left auricle and left ventricle were also made in the posteroanterior position. By rotating the subject into a slight right anterior oblique po-

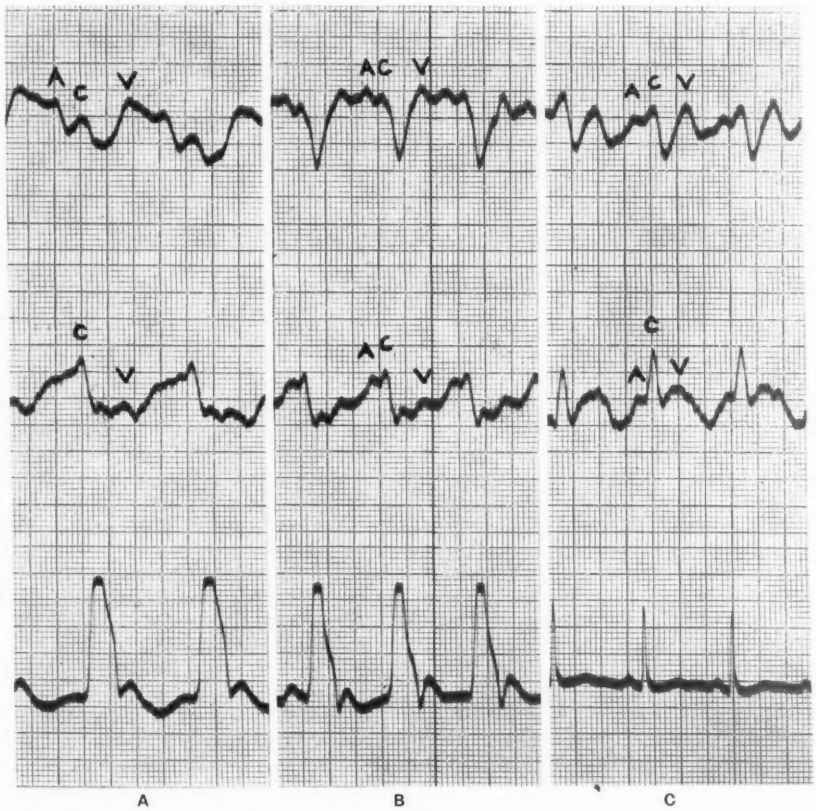

FIG. 2. Simultaneous electrokymograms of the right auricle (top), left auricle (middle), carotid pulse (bottom, 2A and 2B) and Lead II of the electrocardiogram (bottom 2C). The variations in the shapes of the curves in normal individuals is again apparent. The onset of auricular systole of the right auricle can be seen to precede that of the left auricle. (Compare the peaks of the A waves in the upper tracing with those in the middle tracing). The A wave of the left auricle cannot always be recorded (2A). The C and V waves are reflections of ventricular activity and are practically simultaneous.

In the posteroanterior position it was found that tracings of both auricles could always be obtained by placing one photoelectric cell over the lower portion of the right heart shadow and the other cell at the junction of the pulmonary artery and left ventricular contour. In the latter position a tracing of the left sition, tracings of the ascending aorta and pulmonary artery were made. Rotation into the left oblique position made the right ventricular contour accessible anteriorly and the left ventricular contour accessible posteriorly. The carotid pulse tracing was again used in this series for identifying the various waves. Fi-

nally a tracing of Lead II of the electrocardiogram and of both auricles was taken. The major advantage of simultaneous electrokymography is that it does away with the objections which might be raised as to the validity of comparing events occurring in different cardiac cycles by use of a reference point. The measurements obtained by studying 24 subjects in this fashion are tabulated in the table.

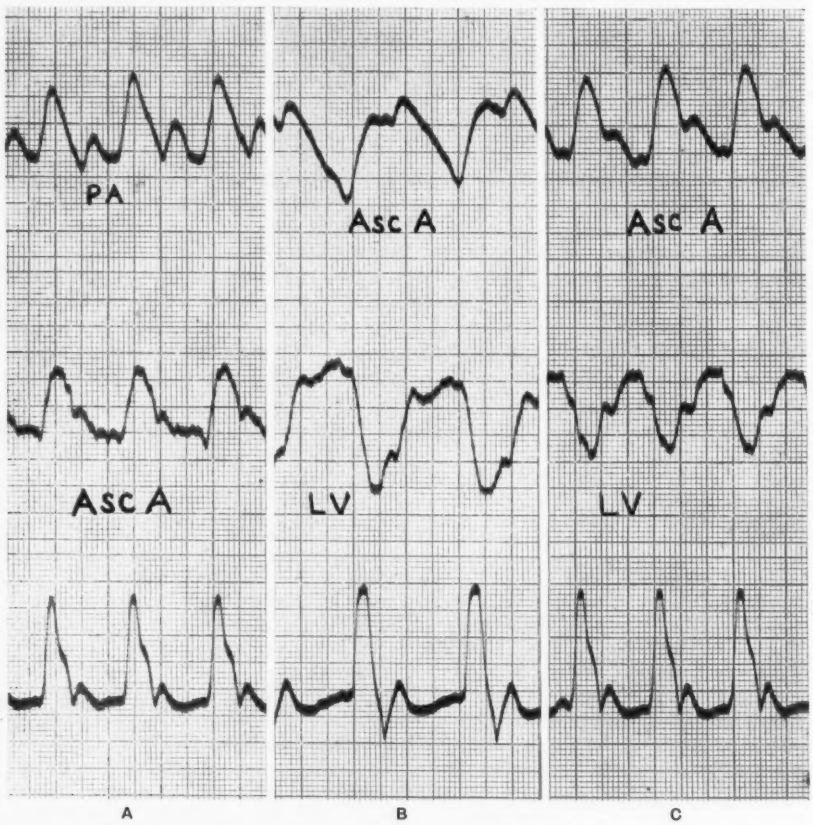

FIG. 3. A. Electrokymograms of the pulmonary artery (PA) and the ascending aorta (Asc.A.). B and C. Electrokymograms of the ascending aorta and the left ventricle (LV).

Figures 1 to 3 illustrate results obtained by simultaneous electrokymography in group 3. In figure 1 the upper tracing is that of the left auricle, the middle was obtained from the left ventricle and the lower tracing is that of the carotid pulse. The contraction of the auricle is marked by the down stroke of the A wave (figs. 1A and 1C), the onset of which is indicated by the peak of the wave. The next event is the closure of the mitral valve which is marked by the beginning of the downstroke of isometric contraction of the left ventricle (fig. 1B). This is reflected on the auricle by the bulging back of the mitral leaflets and the upstroke of the C wave. When the intraventricular pressure reaches the diastolic aortic pressure the aortic valve opens and the ejection phase starts. The opening of the aortic valve is marked by the upstroke of the carotid pulse, the downstroke of the ventricular tracing and is reflected in the sudden drop of the C wave of the auricle. The closure of the aortic valve is indicated by the incisura of the carotid pulse tracing and usually coincides with the end of the systolic downstroke of the ventri-

cle (a correction of .03 seconds must be made in the carotid tracing due to the time required for pulse travel plus instrumental delay). The isometric relaxation phase is inscribed as an upward convexity on the ventricular curve and ends with the opening of the mitral valve indicated by the V wave of the auricle (fig. 1B). Diastolic filling of the ventricle occurs and the cycle is then repeated. It is apparent that with these three simultaneous tracings the events of the left side of the heart can be plotted chronologically.

In figure 2 simultaneous tracings of the auricles are illustrated with that of the right auricle in the upper tracing, that of the left auricle in the middle and that of the carotid pulse in the lower tracing in figures 2A and 2B. In figure 2C an electrocardiogram is substituted for the carotid pulse tracing. It is apparent even on superficial examination that there is a great variation in normal individuals in the exact character of the curves and therefore hasty conclusions as to the presence of valvular disease must not be drawn. The apparent bulging of the auricle in systole illustrated in the upper tracings of figure 1B and 2B is not due to mitral insufficiency but is due to distortions superimposed by the adjacent ventricle and pulmonary artery.

Figure 3A demonstrates the aorta, pulmonary artery and carotid pulses and figures 3B and 3C demonstrate aorta, left ventricle and carotid artery (top to bottom). Because of the great individual variations in the curves obtained by this method we feel that conclusions based on the shape of the curve alone are too subjective to be considered valuable. Objectively one may make observations as to the direction of the curve and time intervals between the various waves.

Results

The measurements obtained from the 53 subjects studied are tabulated in table 1. The last column is a compilation of the data obtained in the three groups with the number of cases in which each particular measurement could be made. The maximum deviation in either direction is included, with a plus sign indicating that the event in the right side of the heart occurred before that in the left. All measurements were estimated to .01 second although the final averages are shown in thousandths of a second. Figure 4 is a composite drawing of the electrokymographic curves ar-

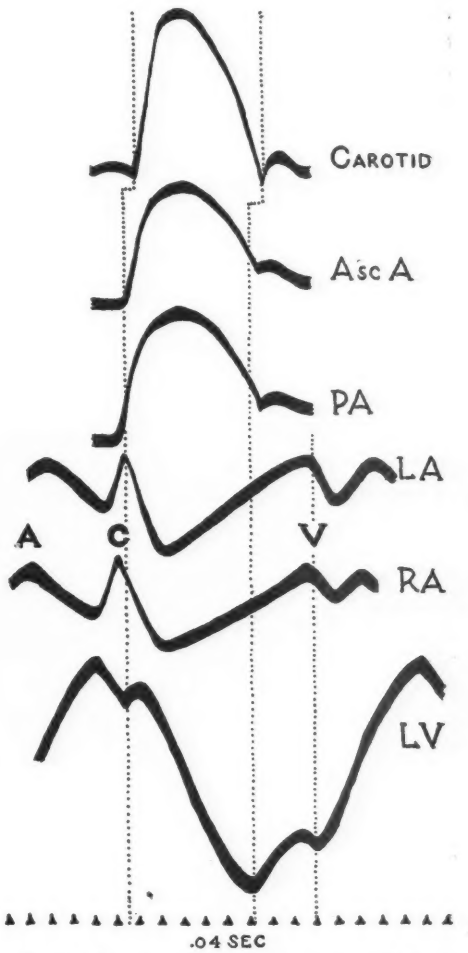

FIG. 4. Schematic diagram of tracings of the carotid artery, ascending aorta (Asc.A.), pulmonary artery (PA), left auricle (LA), right auricle (RA), and left ventricle (LV). The tracings have been drawn to correspond with the average time values indicated in the chart. The dotted lines connect simultaneous points in the left ventricle, left auricle, ascending aorta, and carotid artery. The delay in the carotid tracing is corrected by setting the line .03 seconds to the right.

ranged so that the sequence of events corresponds to the average times obtained.

In terms of the cardiac cycle the data may be interpreted as follows: The right auricle contracts about .02 second before the left. After an isometric contraction phase of .04 second the semilunar valves open, with the pulmonary valve about .01 second ahead of the aortic valve. (This may vary from .03 second before to .02 second after). The systolic ejection phase follows with its duration varying with the pulse rate. After an isometric relaxation phase of .116 second for the left ventricle (varies from .07 to .14 second) the mitral valve opens, with the tricuspid valve opening .025 second ahead of it.

Conclusions

1. Simultaneous electrokymography offers a practical method for timing the cardiac cycle in normal individuals, and for comparing the sequence of events in the right and left sides of the heart.

2. The shape of the curves obtained varies greatly and conclusions as to typical patterns in heart disease must await further evaluation with large series of patients. Objective statements can be made regarding the direction of the heart borders (as reflected on the tracings) and regarding the sequence of events.

3. This method may prove to be of great value in correlating mechanical and electrical events in the heart especially in the presence of conduction defects. In order to establish normal values as a basis for such investigation the present study was undertaken.

Acknowledgments

We are indebted to Dr. Arthur C. DeGraff, Senior Consultant to the Medical Service of the Veterans Administration Hospital, Bronx, New York for his aid and encouragement which made this work possible. We are also greatly indebted to the personnel of the Technicon Company, for the use of their machine, materials, service and technical advice.

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Abdominal Aortic Aneurysm: A Study of One Hundred and Two Cases

By J. Earle Estes, Jr., M.D.

Data were compiled from the records of 101 cases of abdominal aortic aneurysm, almost all of which were due to arteriosclerosis. These records were selected only when there was unequivocal evidence of aneurysm, and cases of true dissecting aneurysm were not included. The data were studied primarily in regard to prognosis of this condition but in addition, all clinical manifestations of abdominal aortic aneurysm were reviewed.

SEVERAL excellent analyses of the clinical and pathologic nature of abdominal aortic aneurysm are recorded. In most of these analyses, the aneurysms were preponderantly syphilitic in nature. The cases which formed the basis of this study were almost entirely those of arteriosclerotic aneurysm and therefore they could be used for comparison with cases of syphilitic aneurysm.

Records of 102 patients having an abdominal aortic aneurysm were obtained from the files of the Mayo Clinic through December 31, 1947. These records were accepted for study only after it was clear that the diagnosis had been established on satisfactory objective evidence. Such evidence included the presence of an expansile, pulsatile intra-abdominal mass in the location of the abdominal aorta, or roentgenographic observations compatible with the diagnosis of aneurysm of the abdominal aorta, or the finding of an abdominal aortic aneurysm at surgical exploration.

Etiology

The criteria for the etiologic diagnosis of abdominal aortic aneurysm were as follows:

1. An aneurysm was considered to be arteriosclerotic in nature if roentgenograms revealed evidence of calcification in the aneurysm, in the abdominal aorta, or in other arteries, or if a clinical diagnosis of arteriosclerosis obliterans had been made.

2. An aneurysm was considered to be syphilitic in origin if there was a positive serologic reaction for syphilis, or clinical evidence sufficient for a diagnosis of syphilis, or both; provided there was no objective evidence of arteriosclerosis of the abdominal aorta.

3. An aneurysm was considered to be due to both syphilis and arteriosclerosis if the criteria designated for each were present.

4. An aneurysm was considered to be traumatic if the role of trauma in development of the aneurysm was likely.

Of the 102 aneurysms considered in this study, 97 were considered to be due to arteriosclerosis. In 35 cases there was no record of objective evidence of syphilis, arteriosclerosis, trauma, or any other etiologic factor. In all except 2 of the 35 cases, however, the patients were of such an age (nearly always more than 50 years and generally more than 60 years) that arteriosclerosis was almost certainly the basis for aneurysm. The 2 youngest of the 35 patients were 42 and 43 years old, respectively. Furthermore, in the total series of 102 patients there were 2 others younger than 42 years who had positive evidence of arteriosclerosis. It seemed reasonable, therefore, to include the aneurysms in all of these 35 cases in the group of 97 considered to be arteriosclerotic in nature. In the case of 2 of the 97 arteriosclerotic aneurysms there was a history of trauma to the abdomen. This trauma was of such dubious nature, however, that the aneurysms were not included in the traumatic classification. In addition to the 97 aneurysms due to arteriosclerosis, there was 1 due to syphilis, 3 to arteriosclerosis and syphilis, and 1 to trauma.

In Kampmeier's[1] series of 73 cases of ab-

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dominal aortic aneurysm, 57.3 per cent of the patients had syphilis. No specific figures were given for the incidence of arteriosclerotic aneurysms but the latter were "very few." Scott[2] reviewed the records of 96 cases of abdominal aneurysm involving the aorta and its branches. He reported the incidence of syphilis as 58.3 per cent, arteriosclerosis 20 per cent, mycotic lesion 18.8 per cent, periarteritis nodosa 1 per cent and tuberculosis 1 per cent. Of the abdominal aortic aneurysms alone, Scott reported that 74 per cent were due to syphilis, 21 per cent to arteriosclerosis and 5 per cent to mycotic lesions. Hubeny and Pollack[3] reviewed the records of 48 cases of "saccular abdominal aortic aneurysm" from the files of Cook County Hospital. They considered that the aneurysms of 75 per cent of their cases were due to syphilis. Eight of the 48 aneurysms were arteriosclerotic. The data in these three reports were based on both clinical and necropsy material. Pratt-Thomas,[4] in a review of data on 17 aneurysms of the abdominal aorta, encountered at necropsy, considered 15 to be due to syphilis, 1 to arteriosclerosis and 1 of indeterminate nature.

The preponderance of syphilitic aneurysms in these studies is clearly manifest. In recent years, however, a growing appreciation of the incidence of arteriosclerotic aneurysms of the abdominal aorta has developed. Blakemore[5] in 1947 reported that of 32 patients with aneurysms in this location admitted in recent years to Presbyterian Hospital, New York, arteriosclerosis was the cause in 26. It seems certain that the aneurysms in the present study were almost always arteriosclerotic in origin.

Age of Patients at Time of Diagnosis

The age distribution of the patients in this study is summarized in table 1. It is apparent that only 27.5 per cent of the patients were under the age of 60 years at the time of diagnosis and only 6.9 per cent were under the age of 50 years. A significant difference may be noted in Kampmeier's patients of whom 67.6 per cent were under the age of 45 years. Also, Scott reported 75 per cent of his patients to be under the age of 50 years.

Incidence of Hypertension

Ninety-four of the 102 records studied contained sufficient information for analysis as to the presence or absence of hypertension. For the purposes of this analysis hypertension was considered to be present if the blood pressure was at least 160 systolic or 100 diastolic, expressed in millimeters of mercury. These levels were used so that the incidence of hypertension would not be appreciably affected by relatively minimal degrees of hypertension. The incidence of hypertension was the only factor in this study wherein a significant difference existed between males and females. Twenty-five of 68 males (36.8 per cent) and 16 of 26 females (61.5 per cent) were hypertensive. The difference in the incidence of hypertension lay in the age group of 60 to 69 years. In this group, 8 of 10 women (80 per cent) had hypertension, while in the same age group only 13 of 33 men (39.4 per cent) were similarly afflicted. It should be recognized, however, that the total number of 10 females in this group is quite small from the statistical standpoint. Other age groups contained relatively similar percentages of males and females with hypertension.

Table 1.—*Abdominal Aortic Aneurysm: Distribution of Patients According to Age at Time of Diagnosis.*

Age, years	Patients	Per cent
40–49	7	6.9
50–59	21	20.6
60–69	47	46.1
70–79	21	20.6
80–89	6	5.8
Total	102	100.0
Mean	65 years	

Symptoms

Abdominal pain and the presence of an abdominal mass that was noted by the patient were the two most frequently encountered symptoms. They were present, respectively, in 37.3 per cent and 25.5 per cent of the 102 patients. It is significant that 31 (30.4 per cent)

of the 102 patients had no symptoms referable to aneurysm (table 2). The aneurysms of these 31 patients were discovered either on physical examination, by a roentgenologic examination of the appropriate region, or by surgical exploration.

Physical Signs

Eighty-eight and three-tenths per cent of the 102 patients had an expansile, pulsatile abdominal mass. A thrill or bruit over the mass was present in 28.4 per cent of the 102 patients. Only 7 patients (6.9 per cent) had no physical findings referable to aneurysm (table 3). Diagnosis in these 7 instances was established by appropriate roentgenologic examination or by surgical exploration.

Table 2.—*Abdominal Aortic Aneurysm: Symptoms*

	Patients	Per cent of 102 patients
Abdominal pain	38	37.3
Abdominal mass	26	25.5
Abdominal throbbing	17	16.7
Backache	14	13.7
Gastro-intestinal symptoms	10	9.8
Shock	8	7.8
Leg pain	3	2.9
None	31	30.4

Table 3.—*Abdominal Aortic Aneurysm: Physical Signs*

	Patients	Per cent of 102 patients
Expansile, pulsatile abdominal mass	90	88.3
Thrill or bruit	29	28.4
Nonpulsatile abdominal mass	3	2.9
Other aneurysm	2*	2.0
Anemia	2	2.0
Abdominal rigidity	1	1.0
None	7	6.9

* 1 patient with a popliteal aneurysm and 1 patient with bilateral fusiform dilatation of the femoral arteries.

Location of Aneurysm as Indicated by Physical Examination

In 84 of the 102 cases, the location of the aneurysm, as indicated by physical examination, was accurately described. Sixty-five (77.4 per cent) of the 84 aneurysms were found in the epigastric (10 cases), umbilical (13 cases), left hypochondriac (23 cases) or left lumbar region (19 cases). Only small numbers of aneurysms occurred in the lower part of the abdomen or in the right side of the abdomen. In addition to the aforementioned 84 cases, there were 8 cases in which the location of the aneurysm was less accurately designated. In 1 of these 8 cases the aneurysm filled the entire right side and in another the entire left side of the abdomen, and in 6 it involved "the entire aorta."

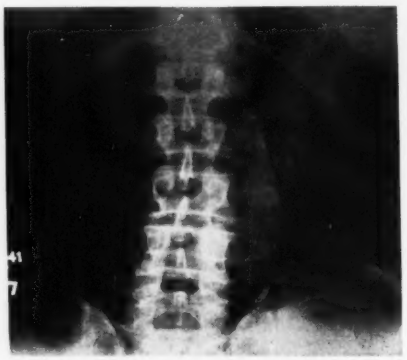

Fig. 1. Anteroposterior view of the abdomen showing a soft-tissue mass (abdominal aortic aneurysm) to the left of the vertebral column with scattered plaques of calcification in the wall of the aneurysm.

Roentgenographic Evidence

Appropriate roentgenograms were obtained in 78 of the 102 cases. In 67 of the 78 cases (85.9 per cent) the roentgenograms disclosed evidence pathognomonic of or compatible with the diagnosis of abdominal aortic aneurysm. In 11 of the 78 cases (14.1 per cent) roentgenograms did not disclose any abnormality. The most prevalent roentgenologic observation was that of scattered plaques of calcification in the wall of the aneurysm or in the aorta. This occurred in 52 of the 67 cases (77.6 per cent). The presence of a soft-tissue mass, aneurysm, or enlarged aorta was the roentgenographic evidence in 36 cases (53.7 per cent). Curvilinear, linear, or laminated calcification was shown in 8 cases (11.9 per cent) and erosion

of bone (vertebra) in 5 cases (7.5 per cent). Displacement of the esophagus, stomach, duodenum, and left ureter occurred in 4 patients, respectively. The types of roentgenographic evidence noted in this study are illustrated in figures 1, 2, 3 and 4. Fluoroscopic examination in suspected cases of abdominal aortic aneurysm was of no significant value except in occasional cases showing displacement of certain viscera after the ingestion of barium.

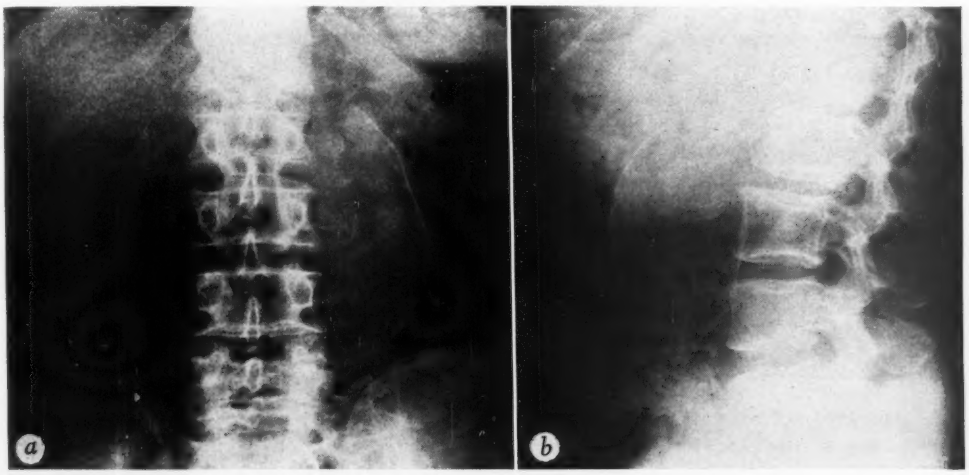

FIG. 2*a*. Anteroposterior and, *b*, lateral views of the lumbar part of the spinal column and the abdomen disclosing a soft-tissue mass with curvilinear calcification.

Blakemore emphasized the low incidence of erosion of vertebral bodies in his series of 32 abdominal aortic aneurysms. There was 1 such instance in his 26 cases of arteriosclerotic aneurysm while there were 4 instances of such erosion in his 12 cases of syphilitic aneurysm. Erosion of bone was present in only 5 of 67 cases referred to in a preceding paragraph.

SURGICAL EXPLORATION

Surgical exploration was carried out in 15 cases; in only 2 of these cases was a therapeutic procedure performed. One of these procedures consisted of wrapping the aneurysm with cellophane. In this case the patient committed suicide after three years because of severe pain. The second patient had partial ligation of the aneurysm with fascia lata. This individual died four years later of myocardial infarction.

The usual finding on surgical exploration was a diffuse aneurysmal dilatation of the aorta which was not considered amenable to surgical repair. Several patients with aneurysms had surgical exploration for reasons other than the

FIG. 3. The esophagus and stomach, containing barium, are displaced to the left by an aneurysm which lies mainly to the right of the vertebral column.

presence of an aneurysm; therefore, surgical treatment of the aneurysms of these patients was not contemplated preoperatively.

the present series) are asymptomatic at the time a diagnosis of abdominal aortic aneurysm is made and, second, it is not always possible

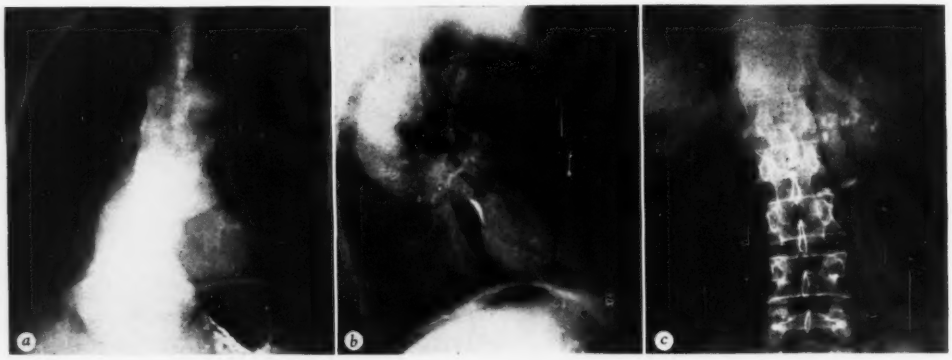

FIG. 4*a*. Anteroposterior and, *b*, lateral views of the thorax and upper part of the abdomen; *c*, anteroposterior view of the abdomen. These disclose aneurysms of the thoracic and abdominal aorta, erosion of the anterior surface of the twelfth dorsal vertebra, and an abdominal aneurysm that contains curvilinear and scattered calcification.

TABLE 4.—*Abdominal Aortic Aneurysm: Survival after the Time of Diagnosis*

Period, years	Patients*		Survived beyond indicated period	
	Total	Patients traced	Number	Per cent of traced patients
1	102	91	61	67.0
2	84	74	43	58.1
3	74	63	31	49.2
4	62	52	14	26.9
5	46	37	7	18.9
8	25	20	2	10.0
10	11	8	0	

* Inquiry as of January 1, 1949. [The one-year group comprises those patients whose aneurysm was diagnosed one or more years prior to the time of inquiry, that is, in 1947 or earlier; the five-year group comprises those patients whose aneurysm was diagnosed in 1943 or earlier, and so forth.]

PROGNOSIS

In this study the prognosis is stated in terms of survival of the patient after establishment of the diagnosis of an abdominal aortic aneurysm at the clinic. It is recognized that the patients may have had an aneurysm for months or years before the diagnosis was made. However, it is very difficult to state prognosis in terms of survival from the onset of symptoms because, first, some patients (30.4 per cent in

to be reasonably certain that an individual's symptoms are due to aneurysm.

Sixty-seven per cent of the traced patients survived one year or longer, following the diagnosis of an abdominal aortic aneurysm at the clinic, 49.2 per cent survived three years or longer and only 18.9 per cent five years or longer (table 4). No patient in this series survived for ten years after diagnosis, but data on only 8 traced patients were available for the study of ten-year survival. The survival rate for the patients who were asymptomatic at the time of diagnosis was no better than the survival rate of patients who had symptoms. The survival rate was much lower than that of the normal population of age 65 years (fig. 5). The latter age was used inasmuch as the mean age of the 102 patients was also 65 years.

The cause of death was ascertained in 49 of the 64 patients known to be deceased. Thirty-one of the 49 patients (63.3 per cent) died from rupture of the aneurysm and 18 (36.7 per cent) died from other causes.

By way of comparison, Kampmeier reported that the duration of symptoms before death was six months or less in 61.3 per cent of 57 patients; twelve months or less in 87.7 per cent, and twelve months to three years in 10.5

per cent. Death was due to aneurysmal rupture in 31 of 38 patients (81.6 per cent). Scott stated that 70 per cent of his 96 patients were dead in thirty-six months and that 17 per cent survived five years. Pratt-Thomas found that the average length of life after onset of symptoms was six months in 14 of his 17 cases.

In 6 of the 102 cases considered in the present study the records were considered to contain unquestionable evidence that the patient's symptoms were due to leakage of the aneurysm. These records were studied from the standpoint of survival after such an incident.

Summary

An analysis of 102 cases of abdominal aortic aneurysm is presented. Arteriosclerosis was the etiologic basis for aneurysm in 97 cases in this series. Only 27.5 per cent of the patients were less than 60 years of age at the time of diagnosis and only 6.9 per cent were less than 50 years of age. The mean age was 65 years. A difference existed between males and females in respect to the incidence of hypertension. This difference lay in the age group of 60 to 69 years, in which 80 per cent of the women and 39.4 per cent of the men had hypertension. The most common symptoms were abdominal pain and abdominal mass, but nearly a third of the patients had no symptoms. The most common physical signs were the presence of an expansile, pulsatile abdominal mass and a thrill or bruit. Roentgenograms disclosed scattered calcification in the aneurysm or in the aorta in slightly more than three-fourths of the cases, and a soft-tissue mass, aneurysm, or enlarged aorta in a little more than half the cases. The

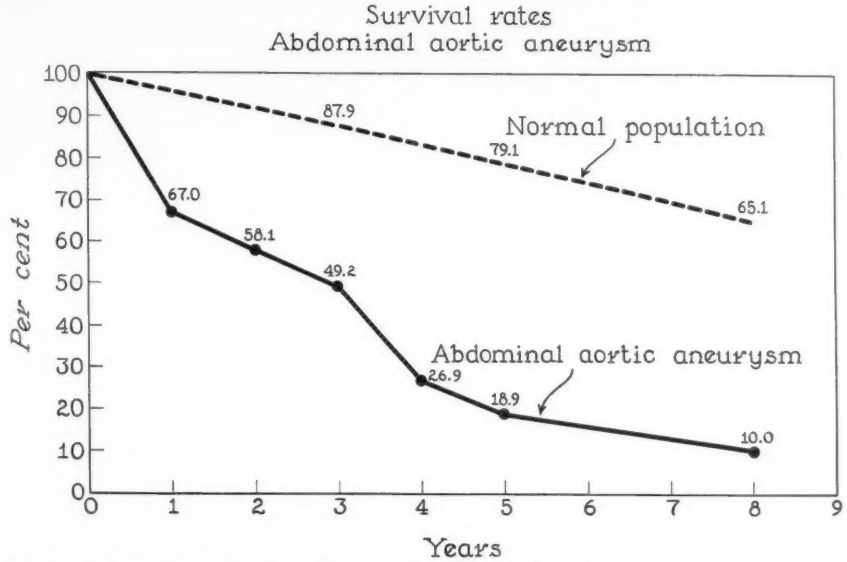

FIG. 5. Survival rates for traced patients who had abdominal aortic aneurysm as compared to the survival rates of the normal population of age 65 years.

A great variation was found but in general the prognosis was poorer than that for the entire series. One patient died on the day of onset of symptoms. One patient survived only five days, 2 survived four weeks, 1 survived six months and 1 survived for four years. The last-mentioned patient underwent surgical exploration because of her symptoms, and a large retroperitoneal hemorrhage was discovered. Surgical repair of the aneurysm was not attempted. She then lived for four years before she died of aneurysmal rupture.*

* I am indebted to Dr. Joseph Berkson and Mr. Robert P. Gage, Section on Biometry and Statistics, for assistance in the compilation and analysis of the data in this study.

survival rate for traced patients was much lower than that for the general population.

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Sodium Gentisate in the Treatment of Acute Rheumatic Fever

By Louis E. Schaefer, M.D., Ira A. Rashkoff, M.D., and Raymond S. Megibow, M.D.

Five patients with acute rheumatic fever were treated with gentisate, the biologic oxidation product of salicylate. The clinical course of this group was contrasted with that of five patients who received salicylate. It was found that, in the doses employed, gentisate had an effect on the symptoms of acute rheumatic fever equal to that of salicylate, but that it produced none of the toxic reactions which were commonly found after salicylate administration. An oral dose of 2.0 Gm. of gentisate, every three hours, continued for at least ten days after the temperature became normal, was sufficient to control the symptoms of the disease.

THE VALUE of salicylates in the symptomatic management of acute rheumatic fever is well established.[1, 2, 3] On the basis of the suggestion that the activity of salicylate depends upon its biologic oxidation product, gentisate, Meyer and Ragan[4, 5] administered this drug to a series of patients with rheumatic fever. They noted that, despite the absence of toxic manifestations, clinical improvement ensued rapidly.

The present report details observations on the effects of sodium gentisate in the treatment of five patients suffering from acute rheumatic fever. In an attempt to evaluate the usefulness of gentisate as an antirheumatic drug, the clinical course of this group of patients has been contrasted with the clinical course of five other patients with rheumatic fever who were treated with salicylates.

Methods and Material

The patients who were to receive salicylate or gentisate were selected by alternation. The diagnosis of acute rheumatic fever was based upon the presence of fever and polyarthritis, and upon the occurrence of cardiac abnormalities, electrocardiographic abnormalities, and a rapid sedimentation rate. All patients were maintained on absolute bedrest. Other than gentisate or salicylate, treatment was identical for the 10 patients. The course of the disease was determined by the clinical manifestations, serial electrocardiograms, white blood counts, and temperature and pulse determinations. Toxic manifestations of salicylate and of gentisate were assayed on the basis of abnormal bleeding tendencies, prolonged prothrombin times, neuropsychiatric abnormalities, gastrointestinal disturbances, and alterations in renal and hepatic function.

Following is a brief resume of the ten patients treated.

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The sodium gentisate was supplied through the courtesy of Dr. R. C. Pogge, Merck and Co., Rahway New Jersey.

Case Reports

Group I. Patients Treated with Gentisate

Case 1, E. G., a 13 year old Puerto Rican boy, had been a resident of New York City for one year. He suffered from frequent sore throats, the last occurring four days before admission, when he also developed pain and swelling of the shoulders, knees, and left ankle. On admission he was acutely ill. The temperature was 102 F., and the ventricular rate was 100. The left ankle, the left foot, the right hip, and the right shoulder were swollen, red, and tender. The heart was markedly enlarged, and systolic and presystolic murmurs were heard over the apex. He was given sodium gentisate, 2.0 Gm. every three hours. After two days of therapy the temperature was normal, and one day later he was asymptomatic and remained so thereafter. The drug was stopped after twelve days. The sedimentation rate, white blood count, and electrocardiogram all became normal within four weeks. Despite a total of 16.0 Gm. of gentisate daily, no evidences of toxicity were apparent. He was well at the time of discharge, after six weeks in the hospital. He was watched by his own physician and by our Follow-Up Clinic, and when last seen by us, seven months after discharge, he was active, in school, and had had no recurrences. The only murmur still present was a soft apical systolic blow.

Case 2, M. P., a 13 year old Puerto Rican girl, had been living in New York City for five years. She had had frequent attacks of pharyngitis in the past. Ten days before admission she developed a sore throat and pain in both feet. At the time of admission she was acutely ill. The ankles and the small joints of both feet were tender, red, and swollen. The temperature was 102 F., and the ventricular rate was 110.

The heart was enlarged and a rough systolic murmur could be heard over the apex. She was given sodium gentisate, 1.25 Gm. every four hours. Twenty-four hours after this treatment was begun, all subjective and objective manifestations of polyarthritis had disappeared. Her temperature was normal after four days. The drug was discontinued after seven days. Four days later her temperature rose to 101 F., and the left shoulder, left elbow, and neck became tender. Gentisate was again given, this time in a dose of 2.0 Gm. every three hours. Three days later she was again both afebrile and asymptomatic. Gentisate was continued for nineteen days, and no further recurrences were observed. The electrocardiogram was normal throughout. The maximum prothrombin time was 15 seconds. There had been no gastric irritation, tinnitus, or deafness. Epistaxis was noted on one occasion during the course of therapy, but since the prothrombin time was 12 seconds at the time, it was felt that this was a manifestation of rheumatic activity rather than of gentisate toxicity. She was discharged to a convalescent home after nine weeks in the hospital, feeling quite well. She has now been there for six months, has had no recurrences of rheumatic activity, and has required no further medication. A soft systolic murmur can still be heard at the apex.

Case 3, J. C., a 14 year old Puerto Rican boy, had suffered from three previous attacks of polyarthritis and fever. A heart murmur had been present for two years. Three days before admission he complained of feverishness, sore throat, and pain in the left knee, right ankle, and right knee. On admission to the hospital his temperature was 102 F., and his ventricular rate was 120. A systolic murmur could be heard over the apex. The involved joints were swollen, red, tender, and warm. He was given sodium gentisate, 1.0 Gm. every four hours. After two days of treatment his temperature was normal, and the signs of polyarthritis had disappeared. During the second week in the hospital, while still on treatment, he developed left maxillary sinusitis. This was accompanied by a rise in the white blood cell count to 14,000. However, no signs or symptoms of rheumatic activity were present at that time. The electrocardiogram, which showed prolongation of the P-R interval on admission, became normal in seven days. The sedimentation rate fell to normal in two weeks. Gentisate was discontinued after three weeks, and he remained well thereafter. The maximum prothrombin time was 14 seconds, and tests for liver, renal, and hematologic abnormalities were negative. He was observed in the hospital for six weeks following cessation of therapy and was well at the time of discharge. He has been examined periodically in the Follow-Up Clinic, and there have been no recurrences during the six months following discharge, although the apical systolic murmur can still be heard.

Case 4, D. A., a 67 year old white woman, had suffered from migratory polyarthritis and chorea in childhood. At the age of 54 she had an attack of arthralgia and fever and was treated effectively with salicylates. Two weeks before admission she developed pain in the left hip and calf, and a rise in temperature to 102 F. For one week her left ankle had been tender and swollen. On admission she was acutely ill. Her temperature was 105 F. Her heart was enlarged and there were systolic and diastolic murmurs at the apex. Her left ankle was red, warm, and tender, and her left hip was quite tender. The sedimentation rate was 65 mm. in one hour. Sodium gentisate was given in a dose of 1.25 Gm. every three hours. One day after treatment was started her temperature was 98.6 F., and a day later all evidences of arthritis were gone. Gentisate was discontinued after seven days. Her temperature rose slightly the next day, and gentisate treatment was reinstituted, this time in a dose of 2.0 Gm. every three hours. This dosage schedule was then continued for eleven days. Her temperature again subsided promptly, and remained normal until her discharge from the hospital three weeks later. Even when the patient was receiving 16.0 Gm. of gentisate daily, the prothrombin time never exceeded 14 seconds, and no abnormal bleeding tendencies or other toxic manifestations appeared. She was well at the time of discharge, and immediately thereafter she returned to work. She was watched by her private physician, and, at the present time, seven months later, she is well and has had no recurrences of rheumatic fever.

Case 5, R. C., a 13 year old white boy, had had several previous attacks of polyarthritis and fever. Two weeks before admission he developed a similar episode and was treated with salicylate for a period of four days. Three days before admission he began to complain of pain in the knees and ankles. On admission the temperature was 100 F. and the ventricular rate 100. The heart was enlarged, and systolic and diastolic murmurs were heard at the apex. The ankles and knees were warm and tender. Sodium gentisate was given in doses of 1.25 Gm. every four hours. The joint symptoms disappeared the following day and did not recur. The temperature, however, remained slightly elevated. Electrocardiographic abnormalities, present on admission, disappeared by the fifteenth day. The white blood cell count was 13,000 on admission and normal ten days later. The sedimentation rate remained elevated persistently. On the fourteenth day of treatment he developed severe pharyngitis with a temperature of 104 F. At this time the white blood cell count rose to 23,500, the sedimentation rate to 105, and the electrocardiogram again became abnormal. There were no joint manifestations, however, at this time. Gentisate was discontinued, and he was placed on penicillin and acetylsalicylic acid, 1.25 Gm. every four hours. The throat infection was controlled in three days, and ten days later the white blood count and electrocardiogram were again nor-

mal. The sedimentation rate, however, remained elevated. The same type of low-grade fever, noted when the patient was on gentisate, persisted while he remained on salicylate, which was continued for forty days. During gentisate administration the maximum prothrombin time was 15.5 seconds, and there was no evidence of toxicity. Significantly, during the period of salicylate treatment, the prothrombin time reached 22 seconds, and the patient complained of deafness and nosebleed. There was no gastric irritation, and there were no chemical or clinical signs of liver or kidney damage. He was discharged to bedrest at home with a low-grade fever. He remained in bed for an additional two months. He was seen in the Follow-Up Clinic five months after discharge, afebrile and asymptomatic, and was then able to return to school. He had received no salicylate or gentisate since leaving the hospital. The diastolic and systolic murmurs were still audible at the apex.

Group II. Patients Treated with Salicylate

Case 6, J. C., a 13 year old white boy, was entirely well until one month before admission, when he developed pharyngitis. Four days before admission he complained of pain in the ankles and fingers. When seen in the hospital, he was acutely ill with a temperature of 103 F. Systolic and diastolic murmurs were heard at the apex. The joints of the right hand and left ankle were red and tender. He was treated with acetylsalicylic acid in doses of 1.0 Gm. every four hours. The joint pains were gone in two days, and the temperature was normal in seven. The white blood count returned to normal in four days, and the initial sedimentation rate of 96 mm. dropped to 15 mm. after twenty-six days. The maximum prothrombin time was 19 seconds. There were no bleeding episodes. He complained of tinnitus during the entire course of therapy, which lasted twenty-nine days. There were no other manifestations of salicylism. He was observed in the hospital for eight weeks after cessation of therapy, and was well at discharge. He was still well, and had had no recurrences, when seen in the Follow-Up Clinic five months later. The systolic and diastolic murmurs, however, were still present.

Case 7, D. F., a 15 year old white boy, had been hospitalized on a previous admission because of acute rheumatic fever. One week before admission he had a sore throat, and four days later he developed pain in the knees and ankles. On admission he was moderately ill, with a temperature of 103 F. and a ventricular rate of 120. The murmurs of mitral and aortic stenosis and insufficiency were present. The left ankle and right knee were warm, swollen, and tender. He was started on acetylsalicylic acid, 1.25 Gm. every four hours. Two days later the joints were normal, and the following day the temperature became normal. The electrocardiogram was normal after nine days. The white blood count fell from 17,000 to 9,800 in fifteen days, and the sedimentation rate dropped from 130 mm. to normal in thirty days. The maximum prothrombin time was 21 seconds, but there were no hemorrhagic manifestations. Because of pronounced tinnitus, the dose of salicylate was reduced to 0.625 Gm. every four hours, and administration was continued for eighteen days. He was discharged at the request of his family on the nineteenth hospital day, and was febrile at home for two months, despite the continuation of salicylates by his private physician. Thereafter, he improved slowly, and, at present, eight months after discharge, he is asymptomatic and engaging in limited activity. The murmurs of both aortic and mitral valvular disease are still present.

Case 8, C. L., a 19 year old Puerto Rican girl, was well until four weeks before admission, when she developed a sore throat. Five days before admission she experienced migratory polyarthritis, involving the joints of the neck, back, knees, and ankles. On admission she was acutely and severely ill, with a temperature of 104 F. and a ventricular rate of 120. An apical systolic murmur was present. Both ankles and both knees were red, hot, swollen, and tender. She was given acetylsalicylic acid, 1.25 Gm. every four hours, and by the following morning all the joints were much improved and the temperature had fallen to 100 F. At this point massive salicylate therapy was instituted and she was given 4.0 Gm. of sodium salicylate every four hours. After a total of 16.0 Gm. she developed nausea, vomiting, tinnitus, a maculopapular rash, a scleral hemorrhage, and a psychosis. The prothrombin time reached 19.5 seconds and the drug was discontinued. The toxic manifestations cleared rapidly, and without reinstitution of therapy the clinical manifestations of the rheumatic process subsided completely. The white blood count returned to normal in six days, the electrocardiogram became normal in ten days, and the sedimentation rate dropped from 125 mm. to normal in twenty-eight days. She was observed in the hospital for four weeks after therapy was discontinued and remained asymptomatic. However, she moved from the city after discharge, and follow-up information was not available.

Case 9, N. S., a 10 year old white girl, was admitted because of the presence of fever and arthritis. At the time of admission she was acutely ill, with a temperature of 103 F. and a ventricular rate of 108. Both ankles were tender, hot, and slightly swollen, and the left knee was tender. She was given acetylsalicylic acid, 1.25 Gm. four times a day. Joint complaints disappeared in three days, the temperature fell to normal in six days, the white blood count of 26,600 dropped to 8,750 in a week, but the sedimentation rate never returned to normal. Salicylate was continued for thirty-six days. Cardiac murmurs were heard during the course of her illness and were still present when the patient was discharged from

the hospital, a week after salicylate therapy was discontinued. The maximum prothrombin time was 21 seconds, but there were no hemorrhages. There was no evidence of gastric irritation, tinnitus, or deafness. Because her sedimentation rate was still rapid at the time of discharge, she was kept in bed at home for four weeks. She was then allowed up progressively, and three months later was able to return to school. At the present time, eight months after discharge, she is completely well, although a systolic murmur is still heard at the apex.

Case 10, H. F., a 17 year old white boy, had an attack of acute rheumatic fever five years previously and was noted at the time to have a cardiac murmur. Two days before admission he developed pain in both feet. When first seen he was acutely ill, with a temperature of 104 F. and a tachycardia at a rate of 104. The heart was enlarged, and the murmurs of mitral and aortic valvular disease were audible. The small joints of the left foot were red and tender. He was given sodium salicylate, 1.25 Gm. every four hours. The joint pain subsided completely in twenty-four hours, and the temperature was normal by the fourth day. The white blood count became normal in five days, and the sedimentation rate in seventeen. Salicylate was continued for fifteen days. The maximum prothrombin time was 14.5 seconds. Because of tinnitus, the dosage of salicylate was reduced to 1.25 Gm. four times per day, with relief of this toxic symptom. He had one nosebleed during his stay in the hospital. There were no recurrences of rheumatic fever after the salicylate was stopped, and he was well at the time of discharge. At the present time, ten months after discharge, he is still well. He is followed both by his private physician and by the Follow-Up Clinic of the Hospital. The cardiac murmurs are unchanged.

TABLE 1.—*Clinical Course following Gentisate and Salicylate Treatment*

Case	Age	Sex	W.B.C.	E.S.R.*	Temp.	Normal After	Pulse	Normal After	ECG	Normal After	No. of Joints	Normal After	Dose in 24 hours
							Gentisate						
					°F.	*days*		*days*		*days*		*days*	*Gm.*
1	13	M	25,000 to 9,200 in 20 days	105 to 19 in 25 days	102	2	100	2	Abn.	15	4	3	16.0
2	13	F	14,700 to 8,100 in 17 days	82 to 20 in 26 days	102	4	110	4	Norm.	—	5	1	16.0
3	14	M	10,000	40 to 13 in 13 days	102	2	120	4	Abn.	7	3	3	5.0
4	67	F	8,150	65 to 20 in 27 days	105	1	110	6	Abn.	8	2	2	16.0
5†	13	M	13,000 to 9,250 in 9 days	101 to 70 in 14 days	100	—	100	5	Abn.	15	4	2	7.5
							Salicylate						
5†	13	M	23,500 to 8,300 in 13 days	105 to 20 in 28 days	104	—	110	5	Abn.	11	0	—	7.5
6	13	M	12,500 to 8,900 in 4 days	96 to 15 in 26 days	103	7	124	5	Norm.	—	4	2	6.0
7	15	M	17,000 to 9,800 in 15 days	130 to 13 in 30 days	103	3	120	3	Abn.	9	2	2	7.5
8	19	F	12,300 to 7,000 in 6 days	125 to 8 in 28 days	104	5	120	4	Abn.	10	4	2	16.0
9	10	F	26,600 to 8,750 in 7 days	125 to 48 in 43 days	103	6	108	6	Norm.	—	3	3	6.3
10	17	M	14,500 to 9,500 in 5 days	90 to 27 in 17 days	104	4	104	4	Norm.	—	4	1	7.5

* In mm. per hour, Westergren method.

† Treated initially with gentisate with moderate response. Developed tonsillitis with reactivation. Treated subsequently with penicillin and salicylate.

DISCUSSION

Table 1 shows the effects of gentisate and salicylate upon certain rheumatic manifestations. It is apparent that both drugs reduce the fever and relieve the joint pains promptly.

Furthermore, the effects of both compounds on sedimentation rate, on leukocytosis, and on electrocardiographic alterations are similar. The uniformly effective response to gentisate suggests that this drug controls the clinical manifestations of rheumatic fever as well as does salicylate. Careful and periodic follow-up examinations ranging from five to ten months are available in nine of the ten patients, and in no case, whether treated with gentisate or with salicylate, has there been a recurrence of rheumatic fever up to the present time.

large doses, a reducing substance appears in the urine. This substance, at least in part, is a glucuronide as determined by the Tollens' test with naphthoresorcinol. Its presence within one to two hours after ingestion of gentisate suggests that this drug undergoes rapid oxidative breakdown in the body. This fact, together with preliminary observations on the gentisate concentration in the plasma,[6] indicates that frequent administration of gentisate is required in order to maintain adequate therapeutic blood levels.

TABLE 2.—*Comparison of Salicylate and Gentisate Toxicity*

Case	Bleeding	Prothrombin Time*	Tinnitus Deafness	Gastric Irritation	Hematologic Abnormality	Urinary Abnormality	Liver Dysfunction	Other
				Gentisate				
1	0	15/12	0	0	0	0	0	0
2	Nose	15/12	0	0	0	0	0	0
3	0	14/12	0	0	0	0	0	0
4	0	14/12	0	0	0	0	0	0
5†	0	15.5/11.5	0	0	0	0	0	0
				Salicylate				
5†	Nose	22/12	Deafness	0	0	0	0	0
6	0	19/12	Tinnitus	0	0	0	0	0
7	0	21/11.5	Tinnitus	0	0	0	0	0
8	Sclera	19.5/12	Tinnitus	Nausea, Vomiting	0	0	0	Psychosis, Rash
9	0	21/11	0	0	0	0	0	0
10	Nose	14.5/12	Tinnitus	0	0	0	0	0

* Undiluted plasma prothrombin time in seconds; the first figure is prothrombin time of the patient, the second is that of a normal control.

† First treated with gentisate, then salicylate.

In regard to toxicity, however, gentisate possesses certain striking advantages over salicylate. This is evidenced by the fact that, following gentisate therapy, we did not encounter any suggestion of gastric irritation, deafness, tinnitus, psychosis, or skin eruption, nor did we observe any marked alteration in prothrombin time. Salicylate administration, on the other hand, was followed almost invariably by some manifestation of salicylism, and usually by a significant increase in the prothrombin time. Neither drug, in the doses employed, produced aberrations in the blood count or abnormalities in kidney function (table 2).

The metabolism of gentisate in vivo is unknown. Following the oral administration of

We have found that 2.0 Gm. of sodium gentisate orally every three hours is sufficient to induce prompt symptomatic and rapid objective improvement. As with salicylates premature cessation of therapy is frequently followed by a recrudescence of complaints, and it is necessary to continue treatment for ten days or more after the temperature has reached normal levels.

CONCLUSIONS

1. In the doses employed gentisate controls the clinical manifestations of rheumatic fever as promptly and effectively as salicylate.

2. An effective dosage schedule is 2.0 Gm. orally every three hours, continued for at least ten days after the temperature becomes normal.

3. Gentisate in the above amounts does not give rise to gastric irritation, tinnitus, deafness, marked prolongation of prothrombin time, rash, psychosis, or changes in blood count, liver, or kidney function.

4. Following the administration of gentisate, a reducing substance appears in the urine which, at least in part, is a glucuronide.

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Studies on Blood Coagulation and the Effect of Digitalis

By GEORGE C. SUTTON, M.D.

Preceding the study of the effect of digitalis upon coagulation of the blood, the reliability of the Lee and White method was determined in 173 normal adults. The effect of digitalis was then studied in cardiac patients before and after compenation and with normal controls in eacgroup: digitalis in clinical doses; addition of heparin to the blood; the heparin tolerance curve; the substitution of methyl methacrylate (Lucite) tubes; liver function as determined by excretion of bromsulfalein; prothrombin times.

METHODS for the measurement of the coagulation characteristics of the blood have been extended and refined markedly in recent years. Studies of the effect of container surface upon clotting[1-6] have led not only to further understanding of the underlying process but to clinical tests based upon prolongation of the coagulation time by certain plastic surfaces. Deceleration of the coagulation of blood in vitro by the addition of heparin has also been developed into a standardized procedure.[7, 8] Similarly, the use of diluted plasma in the prothrombin determination[9-11] and serial measurements of blood clotting time following an injection of heparin, "the heparin tolerance curve,"[12-14] have been employed as means of increasing the accuracy of measurements of small changes in the plasma or blood clotting constituents.

With the use of both the older methods for measuring blood coagulation and these refinements, the results of certain studies on alterations in blood clotting have been at considerable variance. This is well illustrated by investigations of the influence of digitalis on the clotting mechanism. Tanaka,[15] in 1928, reported that parenteral strophanthin shortened the blood coagulation time in dogs. A group of investigators, including Werch,[16] Macht,[17] De Takats and Gilbert,[18] Massie,[19] and Decourt,[20] have presented results in support of this concept that digitalis hastens blood coagulation and have attached clinical significance to this observation. On the other hand, numerous studies, including those of Sokoloff and Ferrer,[21] Moses,[22] Ramsey and Haag,[23] and Taltavull,[24] also made in both experimental animals and human beings, have not been able to verify this purported action of digitalis.

These contradictory conclusions concerning one of the effects of digitalis led to the following investigation. In addition to studying the influence of digitalis upon the rapidity of blood coagulation, an examination of the reliability of the Lee-White test for blood clotting was made.

METHODS AND RESULTS

Standardization and Establishment of the Reliability of the 3-Tube Lee-White Method of Determining Blood Coagulation Time.

Technical Procedure. With a clean dry 5 cc. syringe and size 16 needle, 3.5 cc. of venous blood were withdrawn from an antecubital vein after removal of the tourniquet. Only cases in which there was a clean, easy venopuncture were used. After withdrawal from the vein, the needle was removed from the syringe and 1 cc. of blood was introduced, without frothing, into each of three dry glass Wassermann test tubes resting in a water bath maintained at 37 C. The first tube only was tilted every thirty seconds until complete inversion caused no flow; the second and third tubes were tilted successively in similar manner. The blood coagulation time was calculated to be the time blood first appeared in the syringe until clotting of the third tube. Unless specifically noted, this procedure (blood withdrawal and introduction into test tubes, water bath at 37

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Dr. Harold Davis, Professor of Mathematics, Northwestern University, kindly reviewed the statistical portion of this paper.

C., tube tilting and timing) was employed in all subsequent portions of the investigation.

Subjects. One hundred and seventy-three adult individuals, the majority of whom were ambulatory or clinic patients, or hospital personnel, of Cook County Hospital. All were in apparent good health and receiving no medication whatsoever.

Group I: Sixty adult individuals. The determination was done simultaneously on both right and left arms on two separate days, approximately one week apart. The mean of right and left arm determinations was recorded as the clotting time for each individual.

Group II: One hundred adult individuals. The determination was done on one sample of blood obtained from each person on a single occasion.

TABLE 1.—*Blood Coagulation Times of Normal Individuals Determined by the Three Tube Lee-White Method.*

Group	Group		Range	Mean Time	Standard Deviation
	Min.	Max.			
	Minutes				
I. 60 individuals. Mean time of bilateral determinations					
First Day	7.2	14.2	7.0	10.56	1.7
Second Day	7.7	16.6	8.9	10.44	2.0
II. 100 individuals. Single determinations	6.8	15.6	8.8	10.37	2.1
III. 13 individuals. Repeated (total 99) determinations	6.8	15.6	8.8	10.30	2.2
Mean of Groups I, II, III	7.1	15.5	8.4	10.42	2.0

Group III: Thirteen adult individuals. The coagulation time of single samples of blood was determined on from four to ten random occasions for each individual.

Results. The mean blood coagulation times of the three groups of individuals (I, II and III) totalling 173 in all, who were not receiving digitalis, are presented in table 1. The three test tube Lee-White procedure gave very similar mean times for bilateral determinations, for single determinations on different individuals, and for repeated determinations on a small group of individuals. Each of the three groups had a mean time of approximately 10.4 minutes with a range of 8 to 9 minutes, and a standard deviation of ± 2.0 minutes.

A Study of the Effect of Digitalis as Used Clinically upon the Coagulation Time of Individuals with Organic Heart Disease.

Technical Procedure. Identical to preceding section.

Subjects. Group IV: Sixty adult individuals, predominately male, all with established organic heart disease were selected. All the patients had had a definite episode of congestive failure, during which they had received digitalis leaf (USP XII) in therapeutic doses with definite improvement, and were continued on a daily maintenance dose of the drug at the time of the determination. All individuals were compensated and ambulatory at the time and were receiving no other medication. The mean of simultaneous bilateral arm determinations of the coagulation time was used for each patient. In this group of subjects, as well as in all subsequent groups, unless specifically stated, digitalis was the only drug received by the study group. In all cases the control group was receiving no medication.

TABLE 2.—*Blood Coagulation Times of Cardiac Patients Receiving Digitalis in Maintenance and in Toxic Doses, Determined by the Three Tube Lee-White Method.*

Group	Group		Range	Mean Time	Standard Deviation
	Min.	Max.			
	Minutes				
IV. 60 individuals on maintenance digitalis dosage. Mean time of bilateral determinations	7.2	18.7	11.5	11.9	2.4
V. 10 individuals with digitalis intoxication. (16 determinations)	8.0	16.0	8.0	11.6	2.1
Mean of Group IV and V.	7.6	17.3	9.7	11.75	2.2

Group V: Ten adult individuals, both male and female, with organic heart disease were selected. All the patients had received digitalis leaf (USP XII), crystalline digitoxin or lanatoside C in excessive doses and manifested signs of frank digitalis intoxication (scotomata, anorexia and nausea, diarrhea, pulsus bigeminus). Sixteen determinations were made while the manifestations of toxicity persisted.

Results. The mean blood coagulation times of the two groups (IV and V) receiving digitalis is presented in table 2. The group of 60 cardiac patients who were receiving a maintenance dose of digitalis at the time of the test had a

mean clotting time of 11.9 minutes (S.D = ±2.4 minutes) with a range of 11.5 minutes. In the group of 10 persons with frank digitalis intoxication, the mean coagulation time was 11.6 minutes (S.D. = ±2.1 minutes) and a range of 8.0 minutes.

Both of these groups thus had a coagulation time which was longer than in the control groups (I, II and III) by approximately one and one-half minutes, but this time is less than the observed standard deviation for the procedure.

Effect of Digitalis upon the Coagulation Time of Blood Determined under Special Conditions.

Group VI: Coagulation time of blood to which heparin was added in vitro.

Technical Procedure. One cc. of blood was placed in each of three glass Wassermann test tubes in a water bath at 37 C. The first test tube was dry, the second contained 0.5 cc. normal saline, and the third contained 0.5 cc. normal saline with .005 mg. of crystalline heparin dissolved in it. *All* tubes were inverted three times initially to insure mixing and then every thirty seconds until clotting occurred.

Subjects. Fourteen adult individuals. Control group: 7 normal individuals. Study group: 7 male cardiac patients, all ambulatory and receiving a maintenance dose of digitalis (USP XII), 0.1 Gm. a day.

Group VII: Coagulation time of blood determined in methyl methacrylate (Lucite) test tubes.

Technical Procedure. One cc. of blood was placed into each of three Lucite centrifuge test tubes resting in a water bath at 37 C. and the tubes were inverted successively in the same fashion as the three glass tube Lee-White procedure. The recorded time of coagulation was from the first appearance of the blood in the syringe until the clotting of the third tube.

Subjects. Twenty-two adult individuals. Control group: 11 ambulatory ward patients without cardiac disease. Study group: 11 male cardiac patients who were receiving only either digitalis leaf USP XII (9 cases) or digitoxin (2 cases) in maintenance doses.

Group VIII: Coagulation time of blood in methyl methacrylate tubes and to which normal saline, water and heparin in saline were added.

Technical Procedure. Five cc. of blood were withdrawn as previously described and 1 cc. was placed in each of four Lucite centrifuge test tubes resting in the water bath. The first tube was dry, the second contained 0.5 cc. normal saline, the third 0.5 cc. distilled water, and the fourth contained 0.5 cc. normal saline and .005 mg. heparin. All the tubes were inverted every thirty seconds until clotting occurred.

Subjects: Twenty adult male individuals. Control group: ten ambulatory ward patients with noncardiac complaints. Study group: ten patients with organic heart disease who were receiving maintenance doses of digitalis leaf USP XII.

Results. Measurements of the coagulation time, as determined in glass and Lucite containers, with and without the addition of heparin, of control and of digitalized patients, (Groups VI, VII and VIII) is presented in table 3. Difficulty in determining the precise time of clotting was encountered in those cases where heparin was added to the blood. The main portion of the blood remained liquid, as judged by the streaming of the cells or the motion of occasional minute bubbles, long after the surface of the blood no longer flowed. The times for heparinized blood presented in the chart are the closest approximation to the clotting time of the bulk of the blood, not the formation of the surface film.

TABLE 3.—*Effect of Digitalis upon the Coagulation Time of Blood Determined Under Special Conditions*

Group	Control		Digitalis	
	Mean Time	Standard Deviation	Mean Time	Standard Deviation
	Minutes			
VI. 14 individuals Glass tubes				
Blood	8.4	3.1	7.2	1.9
Blood + saline	6.8	1.7	6.6	1.1
Blood + saline + heparin	35.0	8.1	46.0	10.2
VII. 22 individuals Lucite tubes				
Blood	25.9	5.3	24.5	4.7
VIII. 20 individuals Lucite tubes				
Blood	13.9	3.5	11.3	2.2
Blood + saline	10.0	1.7	8.8	1.0
Blood + water	—	—	8.2	1.8
Blood + saline + heparin	38.6	12.9	49.4	15.0

Comparison of the coagulation times of the control groups and of the groups receiving digitalis revealed that, irrespective of the procedure employed, there was no significant time difference between the two categories.

The Effect of Digitalis in Clinical Dosage upon the Heparin Tolerance Curve.

Technical Procedure. Standard heparin (Lederle) in the amount of 0.15 mg. for each kilogram of body weight was injected intravenously. The blood coagulation time was determined by the three glass tube Lee-White method at 37 C. immediately prior to administration of the heparin and at ten-minute intervals thereafter for sixty minutes. The coagulation time of each sample was plotted graphically against the time after heparin injection. The curve was determined for each individual prior to any digitalis administration. Subsequently, digitalis leaf (USP XII) was given in a quantity sufficient to produce cardiac compensation in those ten individuals with cardiac disease. In general this amounted to a minimum of 18 cat units in ten days to a maximum of 45 cat units in eight days (resulting in digitalis intoxication). In the 3 individuals with neurologic disorders, an average total dosage of 26 cat units in ten days was given. The heparin tolerance curve was determined for each individual after such digitalis administration.

Subject. Thirteen adult male individuals, 10 of whom had compensated organic heart disease, and 3 of whom had neurologic disorders.

Results. In each of the 13 cases studied, the injection of heparin produced a definite transient prolongation of the coagulation time. Comparison of the graphic representation of the individual's response to heparin was made before, and after, the administration of digitalis. Criteria for this comparison were, of necessity, rough. A change was considered to have occurred when the several respective coagulation times forming the peak of the curve, or maximum prolongation of clotting, differed by approximately 20 per cent or more.

In the group studied, no difference in the curve before and after digitalis was observed in 5 individuals. Three subjects showed depressed curves of shortened coagulation times, or a lessened response to heparin, after the digitalis. The remaining 5 had elevated curves of lengthened coagulation times, or an increased response to heparin, after digitalis.

Blood Coagulation and Liver Function before and after Cardiac Compensation.

Technical Procedure. (a) Coagulation Time: Three glass tube Lee-White method identical to that described for Groups I, II and III. (b) Bromsulfalein Excretion: Five milligrams per kilo of body weight were injected and the per cent of retention at 30 and 60 minutes determined. (c) Prothrombin Time: (1) Standard Quick procedure using undiluted plasma and Difco thromboplastin. (2) Prothrombin time of saline diluted plasma (12.5 per cent).

Subjects. Fourteen adult individuals, all male, and all of whom had organic heart disease with unequivocable right heart failure with hepatic enlargement were studied. None of these men had any clinical indications of intrinsic liver disease. Studies were carried out at the time of hospital admission for heart failure, before any medication and, if initally abnormal, after compensation by the use of bed rest, salt restriction, digitalis, and diuretics.

Results. Comparison of the coagulation time, bromsulfalein retention test, and undiluted plasma prothrombin time of the group of fourteen individuals before and after compensation is presented in table 4. The coagulation times before (10.5 minutes) and after (11.2 minutes)

TABLE 4.—*Effect of Cardiac Compensation upon Blood Coagulation Time and Liver Function (Mean results of 14 cases)*

	Coagulation Time (minutes)		Bromsulfalein Retention (% retention)		Prothrombin Time (%) (undiluted plasma)
	Mean	Standard Deviation	30 mins.	60 mins.	
Before compensation	10.5	2.5	30	17	82
After compensation	11.2	1.4	—	—	72

compensation cannot be considered significantly different, for both figures fall well within the normal limits set by the larger control studies. The bromsulfalein retention test was not performed after compensation in all the cases because it was originally within normal limits in all but one case. Determination of the undiluted plasma prothrombin times before (82 per cent) and after (72 per cent) compensation also gave results which are considered to be negative. The state of cardiac decompensation did not per se alter the prothrombin time, nor did the state of improvement, with its attendant therapy, produce any change.

Difficulty was encountered in the use of the prothrombin time of the saline diluted plasma (12.5 per cent) by the Link method. Although the end-point of the test was sharp, repeated determinations on a group of five

normal individuals selected as a control group were scattered so much as to make comparison of the control to any other group difficult. The mean diluted plasma prothrombin time of this small group was 56.5 seconds. Accordingly diluted plasma prothrombin time determinations were not employed in the study of the cardiac patients.

In the analysis of all results, the standard deviation, σ, was calculated according to the formula $\sigma = \sqrt{\frac{\Sigma X^2}{(n-1)}}$ when "X" is the deviation of the observations from the mean, and "n" the number of observations.

Discussion

Comparison of the coagulation times of groups of individuals by means of the three tube Lee-White method gives consistent and reliable results. There is no significant difference between the times obtained by simultaneous right and left arm determinations or single determinations. The daily variation observed in individuals was very close to the range found in single determinations on a group of normal adults. Both tests gave a mean time of 10.4 minutes with a standard deviation of $\pm$ 2.0 minutes. Recognition of this large standard deviation is essential in the interpretation of the results of the test. The coagulation time of an individual must differ by at least twice the standard deviation from the mean in order to be considered probably abnormal. On such a basis normal blood coagulation times would range at least from a minimum of 6.4 minutes, to a maximum of 14.4 minutes. These figures, which are only minimal limits, emphasize the limitations of the determination, the large experimental error and the great individual variation. They also reveal the impossibility of detecting small changes in the coagulation time of either individuals or groups of individuals by means of this method.

This experimental limitation was encountered in the studies on individuals receiving therapeutic digitalis administration. The mean coagulation time of this group was 11.85 minutes; an increase of 13.5 per cent over the control group. This figure falls well within the expected range, however, and cannot be considered a significant variation from the normal. Similarly, the mean coagulation time of the group with frank digitalis intoxication is not significantly different from the control group. These results can be compared with those of Sokoloff and Ferrer[21] in their study of 10 cardiac patients, also using the three tube method. Before digitalization the group had a mean coagulation time of 9.45 minutes and S.D. of $\pm$ 1.55 minutes; during therapeutic digitalization the mean was 9.50 minutes with a S.D. of $\pm$1.41 minutes.

Further examination of the effect of the therapeutic use of digitalis upon the coagulation time of blood under special conditions also revealed no alteration. The coagulation times of the control and digitalis groups determined in both glass and Lucite test tubes, with and without the addition of heparin, showed no significant difference. The prolongation of the clotting time observed when the blood is heparinized or placed in a plastic tube causes the element of surface drying and evaporation to become an important factor in altering the accuracy of the determination. This is shown by the observation that the apparent coagulation time of heparinized blood in a plastic tube was not geater than the time in a glass tube, although it would be expected that the effects would be additive. The increase in the coagulation time with both procedures (plastic container or heparinization) favors the development of a dried surface film which does not flow, although the blood beneath the surface frequently remains liquid. The formation of the film makes the determination of the true clotting time difficult and inaccurate and also emphasizes the importance of the changes of the blood-air surface in blood coagulation time measurements. As the clotting time was prolonged over twenty or twenty-five minutes, ascertaining the end-point became progressively more difficult. Attempts to lessen this drying on the blood-air surface, by stoppering the tube or layering of mineral oil, were unsuccessful.

The heparin tolerance curves before and after digitalis administration revealed no consistent change. This observation is in accord with the work of Moses[22] and others[21] that digitalis as

used in clinical dosage does not alter the heparin response.

The studies before and after compensation were undertaken with the view that cardiac failure and attendant liver engorgement might alter production by the liver of constituents essential for the blood clotting process. Thus improvement of liver function with compensation could contribute to an improvement in the coagulation properties of the blood, quite independent of drug administration. In this control investigation no changes were detected in the blood coagulation time or bromsulfalein excretion before and after compensation. The mean standard prothrombin time of the decompensated individuals was normal.

Satisfactory standardization of the 12.5 per cent saline diluted plasma prothrombin time was not obtained in the control group of five normal individuals. There was considerable variation in the times and the mean for the group was 56.5 seconds. This mean is a rather marked variation from the times of 41.4 and 31.5 seconds obtained by Shapiro[10] and Unger.[25] This discrepancy is, of itself, in accord with some indications that satisfactory comparative standardization of the prothrombin measurement is difficult and that a conservative view must still be taken of the dilution refinement. Fisher[26] obtained a steadily increasing standard deviation with increasing dilution of the plasma used in the test; when 10 per cent plasma was used the average time was 58.4 seconds, with a standard deviation of ±9.1 seconds for his procedure.

Conley and Morse,[27] in a comparative study of the effects of various types of prothrombin-free plasmas and thromboplastins on the prothrombin determination, demonstrated that great variations in the observed prothrombin time are produced by differences in the type of thromboplastin and diluting substance employed. They were able to show that simple saline dilution of the plasma involves not only the relative prothrombin concentration, but the level of other substances involved in the clotting process as well. Using saline as a diluent and Brambel's acetone treated rabbit brain thromboplastin emulsion (Difco), as in this investigation, they found the prothrombin times of all dilutions of plasma below 30 per cent to exceed 35 seconds, and obtained a time of 123 seconds at 10 per cent concentration. The results obtained with the present experiment are interpreted as being in keeping with these views that dilution of the plasma for prothrombin determinations involves more than one factor, i.e., the dilution of prothrombin, and that the value of using diluted plasma for the prothrombin determination is doubtful.

Summary

1. The results of the determination of the blood coagulation times of a group of normal individuals by the Lee-White method and the reliability of this test are presented.

2. Studies on groups of individuals of the effect of digitalis in therapeutic and toxic doses upon the coagulation time of blood determined by several different methods and upon the "heparin tolerance curve" revealed no detectable change from the normal. Change in clinical status from cardiac failure to compensation similarly produced no alteration in blood coagulation times, bromsulfalein retention test and prothrombin times.

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The Use of Digitalis in Spite of the Presence of Ventricular Tachycardia

By J. S. GILSON, M.D. AND F. R. SCHEMM, M.D.

The authors' observations throw some doubt on the validity of objections to the use of digitalis in the presence of ventricular tachycardia. These observations demonstrate that digitalis can be used liberally and that it does not appear to interfere with conversion to a normal mechanism. They suggest that digitalis may even set the stage for reconversion by aiding the failing heart.

THE presence of ventricular tachycardia has been regarded as one of the major contraindications to the use of digitalis.[1–8] Our clinical observations, however, have led us to use digitalis somewhat more freely in cardiac disease in general than is usually recommended.[9–10] The four observations on three patients presented in this paper illustrate instances of the intensive use of digitalis in the presence of ventricular tachycardia.

It is not assumed that the digitalis in these instances stopped the tachycardia, but its use, along with other supportive measures, was followed by marked clinical improvement and the cessation of ventricular tachycardia. These results were not to be expected from the usual literature on digitalis or ventricular tachycardia.[1–8] In our observations signs and symptoms which could be attributed to digitalis intoxication (nausea, vomiting, diarrhea and ventricular tachycardia) disappeared with the intensive use of digitalis, indicating that those signs, including the ventricular tachycardia, were not due to digitalis effect or to digitalis intoxication.

Gratifying experiences[10] with the use of digitalis in patients with disabling ventricular premature beats, heart block, and with severe acute myocardial infarction, all rather commonly regarded as relatively unsuitable conditions for the use of digitalis, led to its use in the first case reported in this paper, when rapidly progressing heart failure seemed to demand digitalis in spite of a persisting ventricular tachycardia.

Observation 1. Case 1: L. G., age 53, a rancher. Admitted May 21, 1940. The tachycardia began thirteen days after admission for symptoms and findings diagnostic of an acute myocardial infarction in an anterior position (fig. 1, 5/22/40). The post-infarction period was characterized by one week of low grade fever, leukocytosis and by recurrent anginal pain up to the onset of the ventricular tachycardia.

On the evening of the thirteenth day following admission (at 8 P.M. on June 3, 1940), after sitting up in bed for the first time that afternoon, the patient noted palpitation and discomfort in the chest with pain. There were no significant physical findings. The rectal temperature was 98.4 F. The heart rate was 128 per minute; the rhythm was regular.

Before the electrocardiogram was read the patient was given 10 cat units of digitalis in twenty-four hours. When ventricular tachycardia was recognized as the mechanism (fig. 1, 6/5/40), quinidine sulfate was administered. A total of 3.5 Gm. was used in forty-eight hours. The quinidine was discontinued when tinnitus, vomiting and a broadening of the QRS complex developed. Because the signs of heart failure were progressive and pulmonary edema developed, digitalis was resumed on the evening of June 7, four days after the onset of tachycardia. A total of 24 cat units was given by vein, with improvement in the signs of failure after 16 cat units and cessation of the tachycardia four hours after the twenty-fourth cat unit, 72 hours after the digitalis had been resumed. The tachycardia had lasted 176 hours, ending at 4 A.M. June 11. Nausea and vomiting ceased twenty-four hours after the ventricular tachycardia had stopped, in spite of the continuation of a maintenance dose of digitalis.

Digitalization was maintained for the next six years until death resulted from another acute myocardial infarction. No subsequent episodes of ventricular tachycardia were observed. The autopsy demonstrated an extensive old, and a smaller recent, infarction.

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Read by title, Twenty-second Annual Scientific Session, Am. Heart Assoc. June 4, 1949.

Comment: As in the other observations which follow, this patient developed his ventricular tachycardia following a myocardial infarction. Unlike the others he had received no digitalis prior to the appearance of the ventricular tachycardia. Quinidine was given to the point of toxic manifestations, yet the tachycardia was unaffected and signs of heart failure were progressing. Digitalis was given primarily because of ominous progression of the heart failure, but it was given cautiously in view of the presence of both an infarction and ventricular tachycardia. The heart failure, the tachycardia, and the vomiting all disappeared with the use of digitalis in full dosage. The patient survived, without recurrence of tachycardia, for six years, during which he received a daily dose of digitalis.

In spite of the free use of digitalis in 87 of 189 cases of acute myocardial infarction seen in the intervening eight years, no other instances of ventricular tachycardia were encountered on this service until 1948. Others which doubtless occurred were probably of too short duration for recognition.

Observation 2. Case 2: J. B., age 72, a retired cattle buyer. Admitted July 8, 1948. The episode of tachycardia began on July 9, 1948 at about 9 P.M., twenty-one hours after admission to the hospital. Admission had followed a two day history of pressure-like chest pains lasting up to three hours and only partially relieved by rest, but totally relieved by morphine. During the first twenty-one hours of admission he was asymptomatic and showed a heart rate of 62 to 69 beats per minute with no irregularity. The blood pressure was 112/68. The lung fields were clear. While reaching for a glass the patient noted a sudden strange sensation, totally dissimilar to his previous anginal pain. He was conscious of rapid beating of his heart, felt giddy, faint, and nauseated. Apprehension was marked.

Four years previously an acute myocardial infarction (fig. 2, 4/21/44) had been associated with a complete heart block and syncopal attacks, which were treated not only with adrenaline, but also with digitalis because of myocardial failure. The heart block disappeared and he was discharged on a "maintenance" dose of digitalis. He had been admittedly somewhat lax in taking it in the intervening four years.

At the beginning of the tachycardia the heart rate was 180 per minute and regular, although the radial pulse was so uneven in force as to simulate auricular fibrillation. This unevenness of the radial pulse was noted in Observation 4 also. Heart tones were dis-

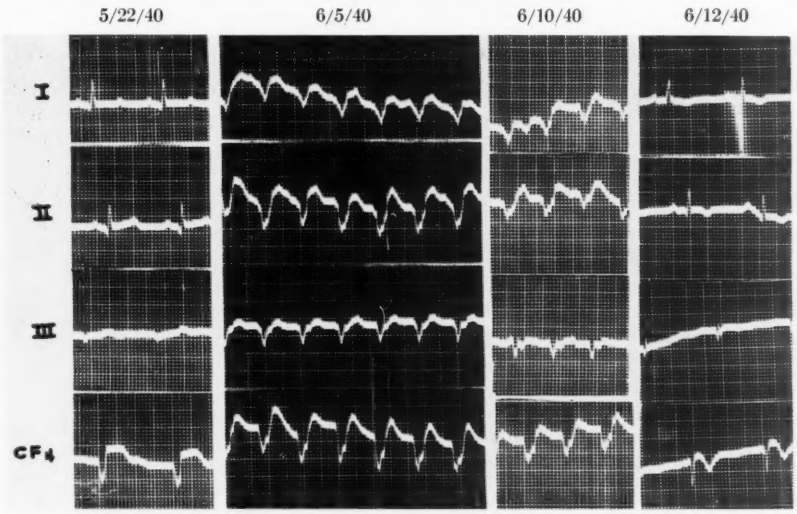

FIG. 1.—Case L. G. Observation 1. The record of 5/22/40 shows a deep Q and elevated S-T segment in Lead CF_4 diagnostic of an anterior myocardial infarction. The next record illustrates the tachycardia; on longer strips the independent P waves could be recognized and calipered out (confirmed by Dr. F. N. Wilson). The third record shows the pattern one day prior to reversal; the last shows the pattern after reversal. In the last record the Q_2 and Q_3 pattern with S**T**-T changes in Leads II and III confirms a posterior infarction as well as the anterior previously diagnosed.

tant. The blood pressure was 102/70. The lung fields were clear.

The electrocardiogram (fig. 2, 7/9/48), taken one hour after the onset, showed a characteristic ventricular tachycardia although clear-cut P waves could not be identified. With the previous case in mind, 0.4 mg. of digitoxin was given intravenously. Thirty minutes later a normal rate had reappeared and a normal mechanism was shown by the tracing (fig. 2, 7/10/48, 8:00 A.M.) together with changes compatible with a posterior myocardial infarction of indeterminate duration. Two hours after this electrocardiogram and twelve hours after the first episode another attack of tachycardia occurred, only

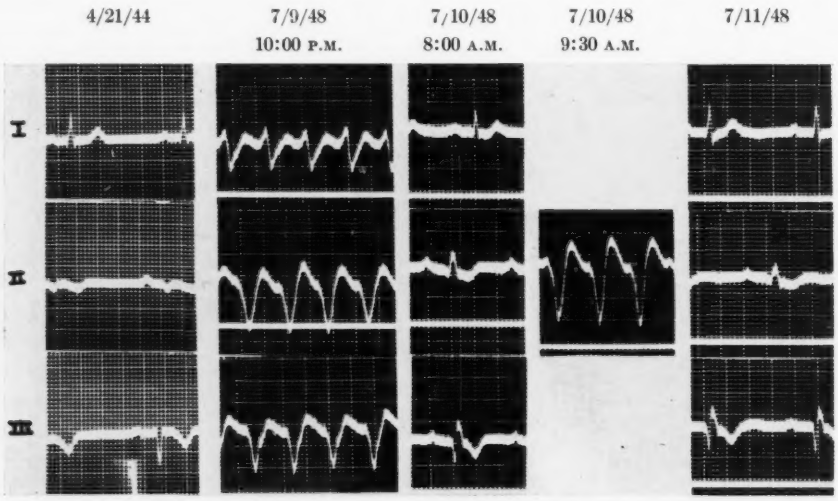

FIG. 2.—Case J.B. Observation 2. The first tracing of 4/21/44 shows a diagnostic pattern for posterior infarction with Q waves, arched S-T and inverted T waves in Leads II and III. The second taken four years later shows the ventricular tachycardia; independent P waves were not identifiable. The 8 A.M. tracing taken ten hours later, on 7/10/48, shows a normal sinus mechanism with a QRS-T pattern in Leads II and III diagnostic of a posterior infarction of recent origin. The fourth record, taken twenty-four hours later, was limited to a long strip of Lead II and shows one of the recurrences of the ventricular tachycardia. The last record shows return to sinus rhythm.

to cease spontaneously in thirty minutes (fig. 2, 7/10/48, 9:30 A.M.).

The patient was then digitalized, receiving 1.0 mg. of digitoxin by vein in 18 hours, in addition to the 0.4 mg. given by vein with the first paroxysm of tachycardia. The nausea and vomiting associated with the attacks subsided during this completion of redigitalization. The following evening, on July 11, after another 0.2 mg. of digitoxin had been given by vein earlier in the day, another episode of tachycardia occurred. The patient was terrified; a reversion to normal rate occurred after morphine was given.

Digitalis was continued without further incident. He was treated as a case of recent myocardial infarction and discharged on his twenty-ninth hospital-day to continue his convalescent care at home. Digitalization has been maintained with from 1.0 mg. to 1.4 mg. of digitoxin per week, faithfully taken. During the past year and a half there has been no recurrence of palpitation or chest pain.

Comment: It seems quite obvious that digitalis neither caused, aggravated nor stopped these intermittent episodes of ventricular tachycardia. They began while the patient was taking a maintenance dose, yet subsided several times in the face of increased dosage. They have not recurred with the increased maintenance dose.

With the first myocardial infarction in 1944, digitalization coincided with the disappearance of heart block and associated Adams-Stokes syncopes. The patient has now survived the original infarction six years and has survived his ventricular tachycardia more than one and one-half years in spite of an increase in his maintenance dose of digitalis.

Observation 3. Case 3:. A T., age 54, crane operator. Admitted Nov. 18, 1948. Extreme palpitation

and malaise, sweating and apprehension, without pain, began about 18 hours before admission.

Fourteen months earlier, in September 1947, a severe myocardial infarction had occurred after one month of anginal pain. A pericardial friction rub persisted for ten days; arrhythmias, including auricular fibrillation and multiple ventricular premature beats, demonstrated by electrocardiogram, occurred intermittently; fever, without other demonstrable cause than the infarction and pericarditis, persisted for one month. Leukocytosis and the elevated sedimentation rate gradually subsided over a 4 week period. The was 23,000. The electrocardiogram showed a ventricular tachycardia (fig. 3, 11/17/48, 3 A.M.)

He was given the usual supportive measures for myocardial infarction, and dicumarol after the diagnosis of a fresh infarction was established. No quinidine was used. On the contrary, he was redigitalized because of our experience in the preceding observations and our belief that patients frequently become insufficiently digitalized on the smaller daily doses of digitalis. Digitoxin, 2.0 mg., was given by vein over a thirty hour period without any effect on the tachycardia. During the entire thirty hours, sweating, ap-

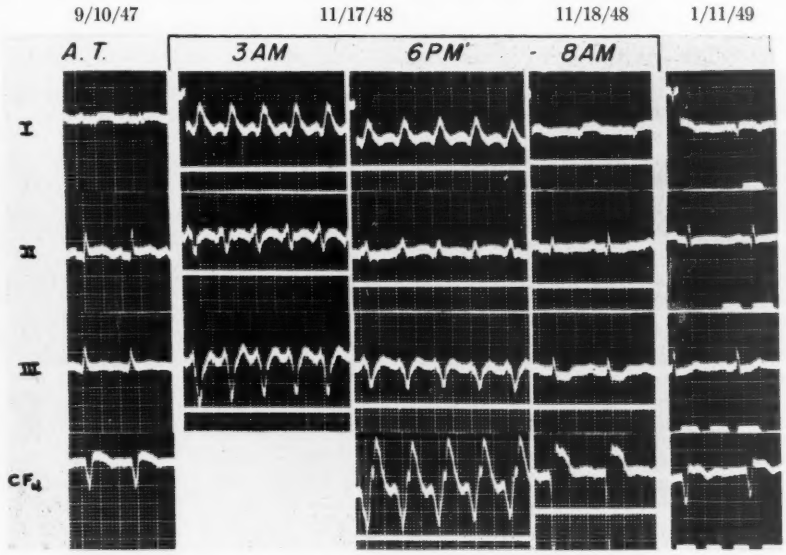

FIG. 3.—Case A.T. Observation 3. The first tracing, 9/10/47, was taken at the time of the original infarction and shows changes in both anterior and posterior myocardial surfaces. The next three records show the episode of ventricular tachycardia, occurring fourteen months later, during which time digitalis was being given. The record of 3 A.M. on 11/17/48 is the tracing taken on admission; that of 6 P.M., fifteen hours later, was taken after 1.8 mg. of additional digitoxin. The record of 8 A.M. on 11/18/48, fourteen hours later, was obtained two hours after the total dose of digitoxin had reached 2.2 mg., a few moments after the mechanism had reverted to normal. The last tracing shows a return to a pattern very similar to that obtained fourteen months earlier.

ECG was compatible with a diagnosis of anterior myocardial infarction (fig. 3, 9/10/47). He was digitalized in the first week and was maintained for the intervening year on 1 cat unit of digitalis leaf taken with religious regularity.

This first episode of ventricular tachycardia began on Nov. 16, 1948, one week after returning to very light work. On examination the temperature was found to be 101.2 F., the heart rate 160 and regular, the blood pressure 120/100. His face was ashen and covered with cold sweat. Respirations were rapid and grunting but the lung fields were clear. The heart sounds were faint and rapid. The white blood count prehension and agitation, and nausea with vomiting persisted despite phenobarbital and morphine. Râles became profuse over the lower lobes of both lungs. Because of the obvious increasing myocardial failure digitalis was continued. Two hours after the next dose of digitoxin which brought the total amount up to 2.2 mg. the mechanism reverted to normal with an apex rate of 90 (fig. 3, 11/18/48, 8 A.M.) Immediately his sweating, apprehension, and nausea ceased. In the next ten hours the râles cleared rapidly; they disappeared in thirty-six hours.

With the reversion to normal rhythm a fresh infarction was suggested by the electrocardiogram

(fig. 3, 9/10/47 and 11/18/48). He was maintained on digitoxin, 0.2 mg. daily, and discharged on the twenty-third hospital day, the hospital program being continued at home.

Comment: We felt certain that this patient had received every dose of digitalis prescribed following the infarction in 1947. During the nine months immediately preceding the ventricular tachycardia he received a "maintenance" dose of 1 cat unit daily. Nevertheless, during redigitalization he tolerated an additional 2.2 mg. of digitoxin given rapidly by vein in thirty hours. Furthermore the symptoms of nausea and vomiting which could have been attributed to digitalis intoxication subsided instantly with the reversion to normal rhythm; this suggested that a therapeutic and not a toxic amount of digitalis had been given. Finally, the ventricular tachycardia itself, which some would feel had been caused by the preceding "maintenance" dose of digitalis, ceased despite the additional "full digitalizing dose" of digitoxin.

Observation 4. Case 3: A. T. (same patient as above). Admitted April 29, 1949.

He had been on markedly restricted activity for six months since recovery from the first attack of ventricular tachycardia and his second myocardial infarction described above. He had been faithfully taking digitoxin, 0.2 mg. daily, since the previous attack.

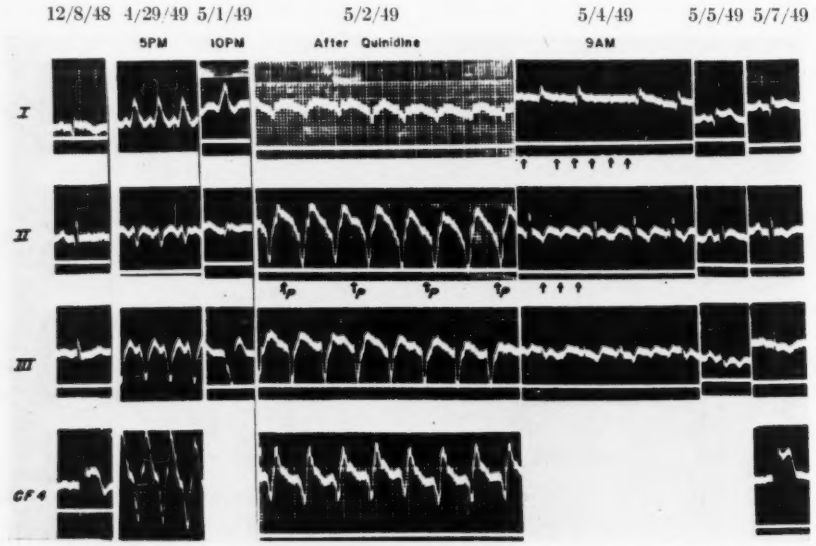

FIG. 4.—Case A.T. Observation 4. The initial tracing on this plate and the final tracing of figure 3 are both interval records between the first and second severe episodes of ventricular tachycardia. The second tracing shows the ventricular tachycardia. The third shows the pattern after 2.6 mg. of digitoxin and prior to the use of quinidine. The tracing of 5/2/49 was taken after two doses of 1.3 Gm. of quinidine; the P waves are clearly seen. The tracing of 5/4/49 shows that the ventricular tachycardia was superseded by auricular flutter (arrows) after totals of 3.7 mg. digitoxin and 5.7 Gm. of quinidine had been given. The next tracing, twenty-four hours later, shows reversion to sinus rhythm. The last tracing shows persistence of the sinus rhythm and also that the QRS-T pattern following recovery from the attack is similar to the pattern preceding the attack.

This second episode of ventricular tachycardia began with palpitation and "uneasiness" about 11 P.M. April 28, 1949 following a quiet visit with two friends. There was no pain.

On examination (April 29) the rectal temperature was 100 F. The heart rate at the apex was 170 and regular, but the radial pulse exhibited irregular force as noted in Observation 2. The heart sounds were of fair quality. No râles were heard at the bases of the lungs. The white blood count was 15,500. The electrocardiogram showed a ventricular tachycardia (fig. 4, April 29, 1949, 5 P.M.).

Because the effect of quinidine, in what was thought to be a third infarction, was feared even more than the effect of digitalis and because the

previous attack of ventricular tachycardia had responded coincident to rapidly given digitoxin in a total dose of 2.2 mg., digitoxin was again given intravenously when morphine and sodium phenobarbital had given no relief. During the first fifty-three hours 2.6 mg. of digitoxin were given intravenously with no effect on the tachycardia. He vomited three times after the first dose of digitoxin but had no nausea or vomiting thereafter. During this fifty-three hour period he became febrile, complained of substernal heaviness, and finally developed pulmonary edema, which subsided in three hours coincident to the use of tourniquets, phlebotomy, and a positive pressure mask. The pulmonary edema recurred sixteen hours later. At this recurrence (just after the record shown in fig. 4, May 1, 1949, 10 P.M.) quinidine lactate* was begun but was halted after 0.4 Gm. had been given because of rapidly increasing irregularity in pulse, cyanosis, and coma. He gradually improved in the succeeding twelve hours.

Although digitoxin was continued, quinidine lactate was again given intravenously on May 2 and 3 (the fourth and fifth days of the tachycardia). Doses of 1.3 Gm., followed in eight hours by 2.0 Gm., and in twenty-four hours by 2.0 Gm. were given intravenously in 5 per cent dextrose solution at a rate of about 0.5 Gm. of quinidine lactate per hour. The heart rate slowed progressively with each administration of quinidine, and an apparent broadening of the QRS complexes and reversal of the major deflections of QRS in Leads I and II occurred. In one record taken during these transient (one to two hours) slowings, P waves are clearly seen at a rate of 68 with a ventricular rate of 150 per minute (fig. 4, May 2, 1949). He became distinctly and progressively irrational during each administration of quinidine; and was controlled only for one to two hours by phenobarbital or morphine. Basal pulmonary râles persisted; cyanosis increased. One Gm. of potassium chloride was given intravenously on the evening of May 3 with no apparent effect.

He had received 3.7 mg. of digitoxin, 5.7 Gm. of quinidine, and 1.0 Gm. of potassium chloride when, on May 4, at 8 A.M., 112 hours after admission and 128 hours after symptoms had begun, his rate suddenly dropped from 200 per minute with a regular rhythm, to 92 with an irregular rhythm, shown by the tracing to be auricular flutter with a variable block (fig. 4, May 4, 1949, 9 A.M.). This occurred twenty hours after the last dose of quinidine and twenty-four hours after the last dose of digitalis.

The next day, five and one-half days after admission, his rhythm was regular and the electrocardiogram (fig. 4, May 5, 1949) showed a sinus rhythm with a rate of 90 per minute. The tracing of May 7, 1949 showed changes indicating a fresh infarction.

Within sixty hours after reversion to normal rhythm his general improvement was marked. Digitoxin, 0.2 mg., and quinidine, 0.6 Gm. daily, were continued as he convalesced uneventfully. In the nine months since his discharge on the thirtieth hospital day, there has been no recurrence of heart failure or tachycardia with 0.6 Gm. of quinidine daily and a heavy maintenance dose of 1.8 mg. of digitoxin per week.

Comment: This patient survived a third myocardial infarction, a second bout of persistent ventricular tachycardia which lasted almost six days, and two episodes of profuse pulmonary edema. It is, of course, impossible to judge with certainty to what extent the numerous adjuncts used (penicillin, vitamins, phenobarbital, morphine, oxygen, quinidine etc.) contributed to the recovery. He did, however, survive, and did revert to a normal mechanism while receiving large doses of digitoxin.

As in the preceding observation the nausea and vomiting, which might have been attributed to digitalis intoxication, cleared in the face of large amounts of additional digitalis. The ventricular tachycardia itself, occurring while the patient was receiving a daily dose of 0.2 mg. of digitoxin, might also have been regarded as a toxic effect of that digitalis dosage. The amounts of digitalis given should, according to widely accepted ideas, have prolonged the tachycardia if the digitalis were a precipitating cause.[1, 3, 4] Yet reconversion occurred at a time when a large amount of digitalis had been given in a relatively short time. If the reconversion occurred as a result of the use of quinidine or any of the other measures employed, at least the digitalis given did not prevent the reconversion.

Digitalis, which is accepted as valuable in the presence of acute myocardial failure with pulmonary edema, may well have determined survival in this case, in spite of the presence of ventricular tachycardia, even if the effect of the digitalis on the myocardium did not indirectly bring about the cessation of the ventricular tachycardia.

Discussion

Authorative interdictions to the use of digitalis in ventricular tachycardia abound in the

* Courtesy of Eli Lilly & Co.

literature. Gold[1] says that there is ". . . only one drug which can abolish it, namely quinidine. Digitalis may make the condition worse. In any case it cannot abolish it." Goodman and Gilman[2] state: "Digitalis should not be prescribed if tachycardia is of ventricular origin." Leaman[4] says: "Digitalis is valueless, in fact it may even increase the rate." And in his therapeutic chart (after ventricular tachycardia) there appears the warning: "Digitalis dangerous." Levine[5] states that, while ". . . in most cardiac conditions in which there is heart failure digitalis is indicated . . . ," the presence of ventricular tachycardia is a special exception and that, "when this arrhythmia is present digitalis will not only fail to improve the situation but may well worsen it." Burch and Reaser,[3] in speaking of digitalis in paroxysmal tachycardia in general, say: "It should be used cautiously, if at all, in the presence of ventricular tachycardia as there is a possibility that the tachycardia will be converted to ventricular fibrillation." A few authorities, however, mention a limited use for digitalis in ventricular tachycardia. Thus, Herrmann and Hejtmancik[6] state that "when digitalis is the precipitating factor (of ventricular tachycardia) it should, of course, be withheld. Occasional cases respond only to quinidine and digitalization . . . and administration of digitalis is indicated in moderate to severe decompensation when it can be ruled out as a causative factor." And White[7] says ". . . Digitalis intravenously . . . should be tried only if other measures in the control of an obstinate attack have failed or if there are symptoms and signs of congestive failure." However, the usual view remains that of Williams and Ellis[8] who warn that "Digitalis is best omitted if it has been used before the attack. Moreover, because we believe that digitalis was a causal factor in some of our cases, we were doubtful of the wisdom of using it in the treatment of an attack even when no digitalis has been taken."

In each of the four observations reported in this paper the ventricular tachycardia occurred following severe injury to the myocardium from a myocardial infarction. In each instance, the clinical picture was alarming and was associated with the characteristic objective findings of severe myocardial injury and a grave prognosis. In the patient who died six years after the observation reported here, the autopsy verified the extensive nature of the myocardial injury. Upon this severe damage in each case were superimposed episodes of ventricular tachycardia, which were prolonged (except in Observation 2 in which the tachycardia was intermittent). In three of the observations the tachycardia occurred while digitalis was in use because of antecedent or coincident myocardial failure. In all four observations the patients received amounts of digitalis after the onset of the ventricular tachycardia equivalent to, if not in excess of, what is commonly considered an average full digitalizing dose. Yet none died during the attack, all reverted to a normal mechanism and all survived their tachycardias for long periods. The reported survival rate is low in ventricular tachycardia: Williams and Ellis[8] show about 35 per cent of 25 cases alive after one month, and Herrmann and Hejtmancik[6] report only 3 out of 8 cases recovering. That death did not occur in the four instances reported here suggests that the digitalis did no harm and may actually have been helpful. If digitalis in proper dosages actually induces ventricular tachycardia the incidence of ventricular tachycardia in our series of cases of acute myocardial infarction should have been high. However, in the nine years from 1940–49, 87 of 189 cases were digitalized both for outspoken signs of congestive failure and for suspected myocardial failure without classical signs.[10] Yet the uncorrected first admission mortality rate was only 10 per cent. There was no increased incidence of ventricular tachycardia as the four observations reported here are the only instances of ventricular tachycardia recognized in the 189 cases.

The fear of digitalis in the presence of ventricular tachycardia appears to have arisen chiefly from the observation that digitalis given continuously in large (presumably toxic) amounts, increases myocardial irritability and can produce ventricular tachycardia in both experimental animals and man. Apparently this led to the assumption that a patient getting the usual, or more than usual, amounts of digitalis has been poisoned by the drug if a ventricular

tachycardia appears. This assumption ignores the fact that the heart disease itself, and particularly myocardial infarction, can increase myocardial irritability and can produce a variety of disturbances of rhythm and rate, including ventricular tachycardia. About half the instances of ventricular tachycardia in many series reported in the literature had received no digitalis at all.

Our observations suggest that the patient may actually need more, rather than less, digitalis if heart failure is present or is developing during a ventricular tachycardia. The tachycardias ceased and the signs of digitalis "intoxication" as well as the symptoms and signs of heart failure disappeared when digitalization was achieved or re-enforced. The beneficial effect of the digitalis in these cases seemed to be in its support of the failing heart. In the first observation the dyspnea and râles began to subside before the tachycardia ceased; in the third observation, the signs of heart failure subsided with redigitalization and the cessation of the tachycardia; and in the fourth observation the two episodes of prolonged profuse pulmonary edema were survived while liberal amounts of digitalis were being superimposed on a liberal maintenance dose.

It cannot, of course, be stated that digitalis actually stopped these tachycardias, yet it seems pardonable to speculate that there may have been some beneficial effect from the digitalis on the uninfarcted portion of the failing myocardium which lessened its irritability and favored the cessation of the tachycardia. In any event it is our impression that a freer use of digitalis for the failing heart in the presence of ventricular tachycardia is justified.

Summary

1. Four observations on three patients with ventricular tachycardia who were given large doses of digitalis are reported. The occurrence of remote and/or recent severe myocardial infarction was established in each instance.

2. In the first observation the patient received 10 cat units of digitalis in two days and, after two days of quinidine, another 24 cat units in three days. In the second observation, 1.4 mg. of digitoxin were given in thirty hours; in the third, 2.2 mg. of digitoxin in thirty hours; and in the fourth, 3.7 mg. of digitoxin in 112 hours. In the last three observations the doses shown were superimposed on "maintenance doses" of digitalis which the patients were receiving when the ventricular tachycardia began.

3. The ventricular tachycardias ceased with, or in spite of, these doses of digitalis. Heart failure was controlled with the digitalis in spite of the presence of the tachycardia. Symptoms, which could have been interpreted as being due to digitalis intoxication, disappeared in spite of its continued use.

4. The observations suggest that digitalis is not as harmful in the presence of ventricular tachycardia as the literature leads one to believe. The survival of these patients for prolonged periods suggests that support of the failing myocardium with digitalis may be an important aspect of treatment in prolonged ventricular tachycardia.

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Liver Function Tests in Chronic Congestive Heart Failure

By LEONARD FELDER, M.D., ALVIN MUND, M.D. AND JULIUS G. PARKER, M.D.

It has been difficult for the clinician to evaluate quantitatively and qualitatively the degree of damage to the liver in the presence of congestive heart failure. This paper gives a statistical analysis of the results of various liver function tests on a group of patients with congestive heart failure. The analysis includes comparisons based on etiology, type of rhythm, duration of heart failure, and nutrition.

INTRODUCTION

ONE OF THE most common manifestations of congestive heart failure is enlargement of the liver. This fact has led several investigators[21, 45, 51, 75, 84] to study liver function tests in an attempt to evaluate hepatic dysfunction in congestive heart failure. Historically, the first association of liver pathology and congestive heart failure was noted by Kiernan[48] who described the "nutmeg liver." Seventy-eight years later Mallory[62] described the typical microscopic appearance of central congestion with focal necrosis. Other authors pointed out the fatty changes[56, 58] and the compression of capillaries by edema fluid accumulated between the liver cell cords and capillaries.[85, 100]

The three main theories of the pathogenesis of the altered liver anatomy are: infection,[62] mechanical compression[14, 100] and hypoxia with secondary nutritional deficiency.[47, 82, 83] The deficiency in oxygen supply to liver cells in heart failure seems to be due not only to the slowing of blood flow through the liver but even more so to arterial unsaturation resulting from pulmonary lesions. This was stressed by Rich[82] and others[2, 47, 57, 83] who pointed out that the jaundice of heart failure is especially apt to develop following pulmonary infarction. Ingelfinger's[43] studies of bromsulfalein removal rates by means of hepatic vein catheterization, and the studies of blood flow to other organs in congestive heart failure[15, 16, 67, 68, 71, 97] make it reasonable to assume that there is a decrease in blood flow to the liver in the presence of cardiac decompensation.

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There is other evidence for impaired liver function in congestive heart failure. Hepatic fibrosis has been found three times as great in patients with heart failure as in patients without heart failure.[13, 30, 42, 46, 96] More significantly, central fibrosis, so common in decompensated cardiac patients, did not occur at all in patients who were not in heart failure. Hyperbilirubinemia has been found in patients who were in severe chronic heart failure.[28] Jolliffe[45] and Cantarow[18] noted that bromsulfalein was not cleared from the blood at a normal rate in the presence of heart failure. Blood cholesterol levels do not seem to be altered by circulatory embarrassment.[12, 18, 80] In a detailed study of 16 patients Jolliffe[45] found some alteration in liver function in 15. Most reports in the literature have utilized from one to five specific liver function tests. Studies have been correlated on the basis of etiology of heart disease, on the type of rhythm present or on the presence or absence of heart failure. The consensus is that there is a severe aberration in liver function in association with a failing heart.

It is the purpose of this paper to show the qualitative and quantitative alteration in liver function tests produced by congestive heart failure; to consider briefly the correlation between pathologic changes and functional alterations revealed by the liver tests used; and to discuss the effects of nutrition, per se, on the metabolic functions of the liver.

CLINICAL MATERIALS AND METHODS

The material for this study was obtained from the case records and pathologic reports of patients attended at the Montefiore Hospital during the five-year period, 1944–48, inclusive. All hospital records of patients on the medical service during

this period were reviewed and only those cases pertinent to the present study were selected. This series consists of 135 cases of which 54 came to autopsy. To be included in the data of this report, a case must have satisfied the criteria for congestive heart failure as set forth by the American Heart Association.[72] The patient must have had congestive heart failure uncomplicated by other disease so far as could be ascertained by examination of clinical and pathologic data.

Under the term "other disease" are included diabetes mellitus, hyperthyroidism, rheumatic fever, subacute bacterial endocarditis, any infectious process, Laennec's cirrhosis or a cirrhotic process of other than cardiac origin. In patients who did not come to autopsy all the clinical and laboratory criteria at our command were utilized in ruling out complicating disease. For the purposes of this report, cardiac cirrhosis was not considered a complication of congestive heart failure.

Although there were no clear-cut criteria employed for evaluating the nutritional status of our patients from the records, an estimate was made on the basis of the subjective impressions of the examiners.

Each of the ten liver function studies was treated statistically in order to permit the recognition of significant differences between specific paired groups; for example, between patients with rheumatic heart disease and those who did not have rheumatic heart disease; between patients with chronic congestive failure of less than three years' duration and those with failure of more than three years' duration; between patients who had auricular fibrillation and those with regular sinus rhythm. The method of statistical analysis used was the standard error of the difference of two proportions.

The total serum protein was determined by the Kjehldahl[17] method; the normal range being 6–8 Gm. per 100 cc. The serum albumin and serum globulin determinations were based on salting-out procedures,[17] the normal ranges being 3.5–5 Gm. per 100 cc. for the former and 1.5–3 Gm. per 100 cc. for the latter. The intravenous 5 mg. per Kg. bromsulfalein test[59, 60, 86, 87] was used; 0–10 per cent retention of dye in the blood after thirty minutes was considered normal. For the cephalin-cholesterol flocculation, the Hanger[39, 40, 69] procedure was employed considering 0–2+ as the normal range. A modified Maclagan[54, 61] thymol turbidity test was used, considering a normal range to be 0–5 units. For bilirubin, the VandenBergh[83] reaction was performed, a range of 0–1 mg. per 100 cc. being considered normal. The Bodansky[3, 9] method for alkaline phosphatase was used; 0–4 Bodansky units was accepted as the normal range. For the cholesterol and cholesterol ester determinations, a modified Bloor[4, 5] method was used and the normal ranges applied were 150–270 mg. per 100 cc. for the former and 60 per cent or more of the total for the latter.

Control Studies. The ten liver function tests used in this study were performed on a control group of 20 presumably normal adults consisting of 10 male and 10 female subjects. The mean values and ranges for each test are given in table 1. The control figures are generally in agreement with those in the literature. However, certain tests show a variable percentage of abnormal values.

Results and Discussion

Thymol Turbidity

We have tested a total of 84 patients on whom 162 determinations were run. In 31 per cent the findings were abnormal (table 2). This

Table 1.—*Results of Liver Function Tests in 20 Normal Hospital Employees*

Tests	No. determinations	% Abnormal	Average	Range
Total protein, Gm. %	20	0	6.8	6.5–7.3
Albumin, Gm. %	20	0	5	4.4–5.3
Globulin, Gm. %	20	0	1.9	1.6–2.4
Cholesterol, mg. %	20	15	183	124–243
Cholesterol esters, % esterification	20	5	72	59–80
Cephalin flocculation, 0–4+	20	10	1+	0–3+
Thymol turbidity, units	20	0	2	1–3
Alkaline phosphatase, B.U.	20	0	1.9	1.2–3.3
Bilirubin, mg. %	20	15	0.56	0.13–1.2
Bromsulfalein, % retention	20	45	11.5	3–26

is a significant figure and is similar to the ones described in the literature. The average value was 4.8 units with a range of 1–15 units. We could find no significant differences in any of the subgroups.

Carter and Maclagan[20] observed that 10 of 28 patients with heart disease had positive thymol turbidity tests. Stollerman[91] noted that 50 per cent of 56 patients with heart disease of all types, with or without failure, gave positive tests. There was only a 36 per cent incidence in those with congestive heart failure, and 6 of 11 patients with acute rheumatic fever showed positive tests. In Stollerman's series most of

those giving positive tests were very weak. The average was 6.7 units.

Ernst and Dotti[26] tested 44 cardiac patients in failure. In 12 patients or 27 per cent the results were abnormal. Of these 44 patients, only 14 had rheumatic heart disease and the incidence of elevated thymol tests in these was three. They also tested 25 patients who were not in failure and found 36 per cent of their tests abnormal.

duration or rhythm was considered. Using 2+ as the upper limit of normal, we found no difference between malnourished and well-nourished patients (table 3).

Kissane, Fidler and Clark[51] reported that 8[illegible] per cent of patients with rheumatic fever and congestive heart failure had abnormal cephalin cholesterol flocculation tests. They used 1+ as

TABLE 2.—*Incidence of Abnormal Findings in 135 Patients with Heart Disease and in 20 Normal Subjects*

Test	Rheumatic		Non-rheumatic		Under 3 years failure		Over 3 years failure		Regular sinus rhythm		Auricular fibrillation		Totals		Controls	
	D.*	A.†	D.	A.	D.	A.	D.	A.	D.	A.	D.	A.	D.	A.	D.	A.
Thymol turbidity	99	28	63	35	67	23	95	29	57	31	105	31	162	31	20	0
Cephalin flocculation	134	26	94	16	90	23	138	21	87	18	141	24	228	22	20	10
Alkaline phosphatase	50	52	28	34	28	32	50	54	33	33	45	56	78	46	20	0
Serum bilirubin	85	53	41	50	48	48	78	54	50	50	76	54	126	52	20	15
Bromsulfalein	19	84	14	86	12	75	21	90	10	80	23	87	33	85	20	45
Plasma cholersterol	73	55	58	28	48	35	83	47	52	35	79	48	131	43	20	15
Plasma cholesterol esters	39	36	22	27	18	33	43	32	22	27	39	36	61	33	20	5
Total plasma protein	83	36	66	20	59	23	90	33	61	21	88	34	149	29	20	0
Plasma albumin	83	28	66	23	59	32	90	21	61	16	88	32	149	26	20	0
Plasma globulins	83	16	66	21	59	20	90	17	61	15	88	20	149	18	20	0

* No. of determinations.
† Per cent abnormal.

TABLE 3.—*Comparative Averages of Liver Function Tests in Relation to Nutritional State*

	Control	Cardiac Failure Series			
		Well Nourished	Mal-nourished	Cirrhotic	Total
Total protein, Gm. %	6.8	6.6	6.5	6.14	6.53
Albumin, Gm. %	5	4.08	3.85	3.63	3.93
Globulin, Gm. %	1.9	2.52	2.68	2.5	2.6
Cholesterol, mg. %	183	190	162	154	175
Cholesterol esters, % esterification	72	66	62	53	63
Cephalin flocculation, 0-4+	1+	1+	1+	1.5+	1+
Thymol turbidity, units	2	4.6	5	5.5	4.8
Alkaline phosphatase, B. U.	1.9	5	6.1	8	5.8
Bilirubin, mg. %	0.56	1.6	2.1	1.7	1.9
Bromsulfalein, % retention	11.5	45	52	40.6	50.7

Cephalin-Cholesterol Flocculation

Our series of 228 determinations performed on 132 patients showed 22 per cent abnormal tests, using 2+ as the upper limit of normal. There was no significant difference in the percentage of abnormal readings when etiology, abnormal. Most observers, however, prefer to disregard any flocculation under 3+.[55, 74] Were we to consider 1+ as abnormal, we would have 40 per cent positive tests instead of 22 per cent. There was a significant difference in all classifications on this basis. The rheumatic patients in failure for over three years, with auricular fibrillation, were much more prone to have positive tests. Using 1+ as the upper limit of normal,

the poorly nourished were also much more likely to have abnormal flocculation.

Alkaline Phosphatase

Sixty-three patients had 78 alkaline phosphatase determinations. Forty-six per cent of these tests showed elevated values. The mean value was 5.8 Bodansky units and the range was between 1.8 and 14.4 Bodansky units. Only 7 determinations were above 10 Bodansky units. According to our material the alkaline phosphatase is one of the more sensitive mechanisms to be impaired by congestive heart failure although the degree of elevation is not remarkably great. There is a significant difference when the groups are broken down into those with auricular fibrillation and those with regular sinus rhythm, although duration of heart failure or etiology does not seem to play any significant role (table 2).

Every attempt was made to rule out bone diseases and extrahepatic biliary tract obstruction[10, 11, 19] Renal insufficiency with secondary parathyroid hyperfunction, however, may contribute to some of the elevations noted.

Only a few reports dealing with the serum phosphatase values in cardiac failure have appeared in the literature. Gutman, and coworkers[34, 35] reported that in 10 patients with chronic passive congestion of the liver, proved at autopsy, 7 had values between 6.7 and 8.6 Bodansky units. None had values over 10 Bodansky units. The alkaline phosphatase values in 3 patients with cardiac cirrhosis varied between 4.4 and 10.9 Bodansky units. In portal cirrhosis the alkaline phosphatase values vary over a much wider range.[29, 32] Gutman and Hanger[35] found phosphatase values below 10 Bodansky units in all of 9 patients with chronic passive congestion of the liver.

Bilirubin

In our series, 52 per cent of 126 determinations on 76 patients showed abnormally elevated serum bilirubin values (table 2). Etiology, duration of failure and type of cardiac rhythm bore no relation to the incidence of jaundice. Next to the bromsulfalein test, the bilirubin determination was the most sensitive of the liver function tests performed. The range was 0.1–13 mg. per 100 cc. with an average of 1.9 mg. per 100 cc. A point of importance is the fact that in 54 autopsied cases, 18 had hyperbilirubinemia. Of these 18, 12 showed pulmonary infarction while 6 were jaundiced in the absence of pulmonary infarction.

The occurrence of jaundice in chronic congestive heart failure is not rare.[7, 27, 36] Both the lungs and the liver are implicated in this complication. In 1910 Oertel[73] named this condition "multiple non-inflammatory necrosis of the liver with jaundice in chronic cyanosis" and ascribed to the liver the chief role in the production of the jaundice. Fishberg[28] emphasized the serious prognostic import of jaundice in heart failure and attributed it to increased red cell destruction. Jolliffe[45] reported a 5 per cent incidence of visible jaundice in 231 cases, there being no apparent relation to the severity of heart failure. Keefer and Resnik[47] found jaundice most commonly in rheumatic patients with auricular fibrillation and long-standing failure. Nine out of their 10 jaundiced patients had pulmonary infarcts. Robertson, Swahm and Konzelmann[84] and White[99] considered serum bilirubin of little importance in the study of cardiac patients.

Kugel and Lichtman[53] carefully studied 424 autopsied cases of primary heart disease. One hundred fifty-one showed pulmonary infarcts. Frank jaundice was present in only 4 per cent of the entire series and 10.5 per cent of those with pulmonary infarction. Only one of the 273 cases without pulmonary infarct had jaundice, but serum bilirubin values were not determined. They stressed the rarity of jaundice in the absence of pulmonary infarction and the importance of the duration of failure and the degree of pulmonary congestion in the development of frank jaundice.

Boland and Willius[13] noted icterus in 14.6 per cent of 75 patients and emphasized the fact that repeated bouts of cardiac failure contributed to the incidence of jaundice. Halsted and Bauer,[37] Meakins,[66] Chavez, Sepulveda and Ortega[21] all report elevated bilirubin values in from 37 to 84 per cent of their patients and again correlate degree and duration of failure with the incidence of jaundice.

Ottenberg[75] summarized what we believe to

be the most rational sequence of events: (1) hypoxic depression of excretory function of the liver; (2) increased production of bilirubin in all infarcted areas; (3) actual central atrophy or necrosis of liver cells; and (4) slowing of the circulation with decreased clearance of blood bilirubin.

Bromsulfalein

This test was performed on the smallest number of patients but gave the highest percentage of abnormal determinations. Thirty patients were tested 33 times and in 85 per cent the findings were abnormal. Using 5 mg. per Kg. of body weight, injected intravenously,[91] we considered a retention of over 10 per cent of dye in the blood after one-half hour as abnormal. Since all of our patients had severe heart failure, no conclusions could be drawn as to a parallelism between bromsulfalein retention and severity of heart failure; nor were any significant relationships noted between retention and the duration of failure or the cardiac rhythm (table 2). The range was 5 per cent to 100 per cent retention.

Our results are in general agreement with previous investigations of the bromsulfalein test in congestive failure. Thus, Jolliffe,[45] using a 2 mg. per Kg. test, found that 75 per cent of his experimental group of patients with heart failure had bromsulfalein retention of 5–20 per cent. With compensation, 66 per cent of them showed normal bromsulfalein removal. He assumed a relationship between changes in liver function, degree of edema, and liver size in congestive failure. Similarly, Bernstein, LeWinn and Simkins,[1] using the 5 mg. per Kg. test in a group of 59 cardiac patients with varying grades of failure, found normal bromsulfalein removal in the absence of failure, and increasing bromsulfalein retention with increasing impairment of the circulation. Chavez, Sepulveda and Ortega[21] similarly analyzed 35 cases of congestive failure and arrived at the same conclusions, although the significance of the differences between their four grades of decompensation is questionable, especially since 50 per cent of the control patients showed abnormal bromsulfalein retention. Blumberg and Schloss[6] studied the bromsulfalein retention (5 mg. per Kg.) in 6 patients who had intrinsic liver disease and cardiac decompensation. They found a rise in bromsulfalein retention as the circulation was impaired, while return of compensation restored bromsulfalein values to predecompensation or normal levels. Ingelfinger[43] catheterized the hepatic vein in human subjects and studied the bromsulfalein "removal rate." He found it to be 10–15 per cent per minute in normal subjects and 6–7 per cent per minute in decompensated patients. Additional data regarding bromsulfalein retention or removal in congestive failure were provided by Cantarow,[18] Meakins,[65] and Robertson, Swahm and Konzelmann.[84]

Cholesterol and Cholesterol Esters

The results of this study (table 2) are based on a total of 131 serum cholesterol determinations of which 56 were normal. Of the latter, 52 were below 150 mg. per 100 cc. and only 4 were above 270 mg. per 100 cc. There is a significant difference only between the rheumatic and nonrheumatic groups, the former having 55 per cent abnormal values and the latter 28 per cent. Each classification or group shows an appreciable percentage of abnormal values.

The cholesterol ester determination was performed 61 times. There was a 33 per cent incidence of low values. This is fairly constant for each of the groups tested. Eighty per cent of the abnormally low esters were associated with low total cholesterols.

Plasma cholesterol has been thoroughly studied, as indicated by the extensive review of Weinhouse[98] in 1943. In spite of a tremendous volume of work, there is practically no direct reference to changes in blood cholesterol and its ester fraction in congestive heart failure. However, Weinhouse, quoting Bodansky and Bodansky[12] and Port,[80] states that in cardiac patients with edema there is no increase in blood cholesterol.

In contrast to the paucity of data in congestive failure, there is abundant material dealing with blood cholesterol changes in various types of heart disease. Poindexter and Bruger[79] observed that cholesterol values were low in patients with rheumatic heart disease

and elevated in patients with hypertensive and arteriosclerotic disease. They found no difference in the ratio of ester-free cholesterol in the three types of heart disease. On the other hand, Elliot and Nuzum[24] found no hypercholesteremia in uncomplicated arterial hypertension, vascular degeneration or renal impairment complicating hypertension. This latter point of view was substantiated and extended to include all the lipid fractions by the work of Page, Kirk and Van Slyke[76] who studied a group of 16 patients with uncomplicated essential hypertension. By contrast, the reports of Gorham and Myers[31] and Davis, Stern and Lesnick[23] support the findings of Poindexter and Bruger showing a hypercholesteremia in arteriosclerotic cardiac patients. There is considerable overlap between the figures for arteriosclerotic patients and normal subjects.[89] If cholesterol metabolism is disturbed in congestive failure, the etiology of the heart disease must be considered in some relation to this disturbance, as emphasized in two recent reviews.[22, 33]

Our own results substantiate the reports by Poindexter and Bruger[79] of significant differences of the blood cholesterol level in patients with rheumatic heart disease and those with nonrheumatic heart disease. Since rheumatic heart disease is acquired earlier and cardiac decompensation usually occurs at a much younger age than hypertensive or arteriosclerotic heart disease, the question arises as to whether age is a factor in changing the blood cholesterol. However, Page and his associates[77] in a very careful statistical analysis showed that variations of age, from 20–90 years, were not found to have a determinable influence on either the amount or the composition of plasma lipids.

It must also be emphasized that patients with rheumatic heart disease are in congestive failure for longer periods and suffer greater degrees of malnutrition than patients with hypertensive or arteriosclerotic heart disease. Man and Gildea[64] in a study of the serum lipids in malnutrition found that the cholesterol varied with the state of nutrition, increasing with improvement in nutrition.

Finally, the factor of active infection must be considered in patients with rheumatic fever. Thus, King and Bruger[49] report subnormal serum cholesterol values in tuberculosis. Stoesser[93] observed a low ester fraction in children suffering from pneumonia and acute upper respiratory infections. Kipp[50] reported the same for pneumonia in the adult. Knudson, Ordway and Ferguson[52] found marked depression of the cholesterol ester fraction in patients with a positive Wassermann, despite no change in the total cholesterol level.

Total Plasma Proteins, Albumin and Globulin

We had 149 total protein determinations performed on 104 patients. Of these tests, 29 per cent were abnormal, i.e., below 6.0 Gm. per 100 cc., but excluding values above 8.0 Gm. per 100 cc., in which the elevation was due solely to hyperglobulinemia and of which 6 are included in the abnormal globulin series.

As indicated (table 2), 36 per cent of the tests in the rheumatic group and 20 per cent in the nonrheumatic group were abnormal. This difference is statistically significant. On the other hand, there is no significant difference between groups analyzed with respect to duration of failure and the type of cardiac rhythm.

As for albumin determinations (table 2), 26 per cent of the determinations were abnormal, i.e. below 3.5 Gm. per 100 cc. Patients with auricular fibrillation showed 32 per cent abnormal determinations, while those with regular sinus rhythm were significantly different, having only 16 per cent abnormal determinations. There was no significant difference when etiology or duration of failure was considered.

Of 149 globulin determinations (table 2), 18 per cent were abnormal, i.e., above 3.1 Gm. per 100 cc. However, four values of 0.8, 0.7, 1.2 and 1.3 Gm. per 100 cc. were not included among the abnormal values. No significant differences were noted when groups were compared on the basis of etiology of heart disease, duration of failure, or type of cardiac rhythm.

The average plasma protein values were as follows: total proteins 6.59 Gm. per 100 cc., with a range of 4.0–8.9 Gm.; albumin 3.93 Gm. per 100 cc., with a range of 2.4–5.5 Gm.; and globulin 2.65 Gm. per 100 cc., with a range of 0.7–4.6 Gm.

A direct correlation was generally noted be-

tween downward aberrations of total protein and of albumin values. Conversely, a high total protein figure was invariably a reflection of hyperglobulinemia. There is rather universal agreement on these correlations among previous investigators.

Ellis,[25] Hand,[38] Herrmann,[41] Thomson,[95] Moore and Van Slyke,[79] Rowe,[88] Payne and Peters,[78] and Biorck and associates[3] found low total plasma protein and plasma albumin values in patients with congestive heart failure. Stewart,[92] however, found a normal specific gravity of the plasma in cardiac patients but made no chemical analyses. Thomson[95] found in patients with cardiac decompensation an average total protein of 5.28 Gm. per 100 cc.; albumin, 2.69 Gm. per 100 cc.; and globulin, 2.59 Gm. per 100 cc. Similarly, Payne and Peters[78] found that 13 of 24 patients in congestive heart failure had total protein values below 6.2 Gm. per 100 cc. Herrmann[41] found that 100 patients in failure averaged 6.10 Gm. per 100 cc. for total protein with albumin of 3.54 Gm. per 100 cc. (subnormal by his standards) and globulin of 2.58 Gm. per 100 cc.

The factors playing a part in the development of abnormal protein values in chronic congestive heart failure are somewhat difficult to evaluate without adequate metabolic studies in view of the dynamic equilibrium of proteins in the body fluids.[90] Herrmann[41] noted the lowest plasma protein levels in patients who had had congestive failure for many months, especially in those with clinical evidence of cardiac cirrhosis. Thomson[95] believed that the low protein and particularly the low albumin values were due to malnutrition. Only a broad general correlation can be drawn from our data between the duration of the congestive heart failure, the impaired state of nutrition, and the depression of total protein and albumin values. Since our patients are a selected socio-economic group with chronic congestive failure, rather than acute or recurrently acute failure with long periods of remission, it is virtually impossible to decide which of the following factors play the most important roles: (1) cardiac failure, per se; (2) inadequate protein and caloric intake; (3) interference with protein formation. The poor appetite of patients in chronic congestive failure is well known.[44] There is little doubt that they suffer from insufficient protein intake. This is the only factor of which we can be certain.

Nutrition

The method employed in this survey was to record the observation of the admitting physician as to whether the patient was well nourished or poorly nourished. We were well aware of the fallacies in such measures but were not prepared to use more objective tests for nutrition. The results of various liver tests in different states of nutrition are shown in table 3.

It is significant that 54 per cent of our patients were considered to be poorly nourished. The longer the duration of heart failure, the greater the number of malnourished patients. Rheumatic patients and those with arrhythmias were more emaciated than those with other types of heart disease and those having normal sinus rhythm, perhaps because rheumatic heart disease patients live longer with cardiac symptoms.

Certain plasma constituents seem to be directly correlated with diet. Among these substances we have measured the cholesterol and protein fractions. Our findings are consistent with those of other studies.[21, 41, 61] The average serum cholesterol was 175 mg. per 100 cc. in the entire cardiac group; in those patients who were malnourished, the average was 162 mg. per 100 cc. compared to a level of 190 mg. per 100 cc. for the well nourished.

The average value for total proteins in the entire series was 6.59 Gm. per 100 cc. This is considerably higher than those of other observers.[41, 78, 95] The well nourished patients averaged 6.6 Gm. per 100 cc. as compared with a 6.5 Gm. per 100 cc. level for the poorly nourished. Serum albumin averaged 3.93 Gm. per 100 cc. In the well nourished it was slightly above at 4.08 Gm. per 100 cc. and in the malnourished 3.85 Gm. per 100 cc. Globulin levels averaged 2.65 Gm. per 100 cc., but were slightly higher in the malnourished than in the well nourished, 2.68 Gm. per 100 cc. and 2.52 Gm. per 100 cc., respectively.

There is marked individual variation in these tests and no definite conclusions can be drawn

from the single case. Although there is an apparent correlation between the state of nutrition and the changes in the serum protein level, these changes are not statistically significant.

Cardiac Cirrhosis

The type of liver function impairment noted in a group of patients with proven cardiac cirrhosis is shown in table 3. It must be emphasized that the data recorded are based on a small series of 14 cases, having a maximum number of 47 determinations for the cephalin flocculation test and a minimum of 6 for the bromsulfalein determinations.

The results show, furthermore, that there are more abnormal determinations with each of the liver function tests in the cardiac cirrhotic patients as compared with the over-all group of cardiacs; the most significant changes occurring in the total proteins and albumin values of which the percentage of abnormal values is doubled in the cirrhotic group compared with the over-all cardiac group.

A comparison of the mean values and ranges in this cirrhotic group with those of the total observed group shows that the trends and actual values are almost the same. The only real differences to be noted are that the alkaline phosphatase reaches the relatively high value of 8 Bodansky units while the cholesterol and cholesterol esters are about 10 per cent lower in cirrhotic patients than in the total group of patients.

Conclusions and Summary

Ten liver function tests were evaluated in a study of 135 cases of chronic protracted congestive heart failure of which 54 came to autopsy. Two or more different tests were performed on each patient; 50 per cent of the patients had seven or more tests performed. Seventy-four per cent of the patients had at least one abnormal determination although only 30 per cent of the tests performed were out of the normal range. The greater the variety of tests made, the higher was the incidence of abnormality.

No significant differences were found when the etiology of the heart disease was considered, nor did the duration of heart failure or type of rhythm alter the liver function tests. The nutritional status of the patients was considered grossly, and, except for showing the expected shifts in average determinations, did not affect the results of the liver function tests significantly.

The thymol turbidity test was abnormal in 31 per cent of the tests. Cephalin flocculation was abnormal in 22 per cent of the determinations and showed a slight increment in the malnourished group of patients.

Alkaline phosphatase was elevated in 46 per cent of the determinations in the group as a whole and in 83 per cent in the cases of cardiac cirrhosis which were autopsied. There was no significant difference noted on the basis of nutrition.

Bilirubin was found to be elevated in 52 per cent of the tests performed. Sixty per cent of the cases with cardiac cirrhosis had abnormal values.

Bromsulfalein clearance was abnormal in 85 per cent of the determinations.

The serum cholesterol values were found abnormal in 43 per cent of all determinations and there was a significant difference between the rheumatic and nonrheumatic groups. The abnormal values were below 150 mg. per 100 cc., four determinations being abnormally high. The well nourished cardiac patients averaged 190 mg. per 100 cc. The poorly nourished patients averaged 162 mg. per cent, and the autopsied cases with cardiac cirrhosis averaged 154 mg. per 100 cc.

The cholesterol ester values were abnormal in 33 per cent of cases, but there were no significant differences between any of the cardiac groups. The values tend to parallel the cholesterol figures.

The total plasma proteins were found to be quantitatively abnormal in 29 per cent of the determinations. The average was 6.53 Gm. per 100 cc. The well nourished patients averaged 6.6 Gm. per 100 cc. as against 6.5 Gm. per 100 cc. for the malnourished and 6.14 Gm. per 100 cc. for those with proven cardiac cirrhosis.

The average albumin was 3.93 Gm. per 100 cc., and 26 per cent of the patients had less than 3 Gm. per 100 cc. The values for the well nourished patients averaged 4.08 Gm. per

100 cc., for the malnourished 3.85 Gm. per 100 cc. and for the autopsied cirrhotic patients 3.63 Gm. per 100 cc.

Plasma globulin was elevated in 18 per cent of the patients. The average was 2.6 Gm. per 100 cc.

The possible mechanisms involved in the observed liver function abnormalities are discussed. The conclusion is drawn that since the liver is multifunctional a proper evaluation requires a multitude of tests. It is to be hoped that future studies utilizing the clearance technic and other specific methods will localize the exact site of anatomic damage.

On the basis of tests performed, there is apparently no pathognomonic pattern of impairment of liver function in congestive failure and cardiac cirrhosis. There is definite impairment of liver function in congestive heart failure. The exact basis for this change remains unknown.

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Pericardial Effusion Mistaken for Cardiac Enlargement in Severe Anemia

Report of Two Cases

By Louis A. Soloff, M.D., and C. T. Bello, M.D.

Anemia is sometimes the sole cause of enlargement of the so-called cardiac silhouette. Successful treatment of the anemia may then restore the silhouette to normal. The enlargement has been attributed to cardiac dilatation. Because of the recognized difficulty in distinguishing pericardial effusion from cardiac dilatation, direct puncture was attempted in two instances of anemia with the silhouette enlarged presumably due to dilatation. In each instance, the enlargement was demonstrated to be due almost exclusively to pericardial effusion.

THE HEART in anemia has been recently the subject of several comprehensive reviews.[1, 2] There is therefore no need at this time to discuss this subject in detail. It is well known that the heart is frequently involved and that symptoms and physical signs present in anemia may mimic those of organic heart disease. Individuals with anemia may complain of dyspnea and palpitation on effort, weakness and dizziness. Dyspnea is usually not present at rest. Precordial pain identical with angina pectoris may occur. Slight and later a marked degree of sacral and dependent edema may be present. The heart rate is rapid. Murmurs are frequent; the commonest is a systolic murmur at the apex. Later, systolic basal murmurs and systolic murmurs widely distributed over the precordium occur. Even a diastolic murmur, usually over the aortic region, may be audible in severe anemia. Electrocardiographic abnormalities such as low amplitude, S-T segment depressions and low, flat and even inverted T waves are noted. Finally, the heart is enlarged by clinical examination. Roentgenologic examination confirms the enlargement that is sometimes massive.

Cardiac hypertrophy has been demonstrated at necropsy in both clinical and experimentally produced anemia with no apparent other cause. The hypertrophy is usually not marked. The enlarged hearts in anemia demonstrable by roentgen study which become smaller under treatment are regarded as being due in greater measure to cardiac dilatation, because it is doubtful that hypertrophy alone can produce massive enlargement of the cardiac silhouette. Ball[3] was the first to demonstrate by roentgenographic technic marked enlargement of the cardiac silhouette that disappeared after adequate therapy. These findings have been amply confirmed by others.

The difficulty in differentiating by roentgenographic technic cardiac dilatation from pericardial effusion is well known. The purpose of this report is to record two instances of anemia with massive pericardial effusion in which an erroneous clinical and radiologic diagnosis of massive cardiac enlargement due to anemia had been previously made. One individual was a girl with erythroblastic anemia. The other was a woman with pernicious anemia. These cases demonstrate that pericardial effusion may occasionally be the sole or major factor in the enlargement of the so-called cardiac silhouette in anemia.

Case Reports

Case 1: L. L. was first admitted to Temple University Hospital January 17, 1940, and after 13 succeeding admissions, died February 2, 1944, at 19 years of age. She had been anemic since birth. She had been given repeated small transfusions all of her life. Her admission for the first time to Temple University Hospital was for several transfusions because of severe anemia, fatigue, repeated epistaxis, anorexia, dyspnea and palpitation on effort.

Physical examination revealed a pale, undernourished Greek girl with bronze colored skin, pre-

From the Department of Medicine, Temple University Medical School.

su nably that of hemochromatosis. The blood pressu e was 120/60. The pulse rate averaged over 100 pe minute. The heart appeared enlarged to the an terior axillary line and remained so on subsequent ex minations. A systolic murmur audible all over th precordium and a diastolic murmur heard only ov er the aortic region were noted on all admissions. Sh e was treated by multiple blood transfusions. Th e subsequent admissions were all for blood transfu ions except for the last on January 26, 1944, wh en she was admitted for heart failure. This time sh e was orthopneic and had distended neck veins. She died five days later.

The hemoglobin and red blood cell count during her various admissions varied from 4 Gm. hemoglobin and 1,700,000 red blood cells to 10 Gm. hemoglobin and 4,370,000 red blood cells. It is interesting to note that only once did the liver appear

FIG. 1. L. L. Roentgenogram of the chest showing huge so-called cardiac silhouette.

to be normal in size. The liver was apparently normal in size when the hemoglobin and red blood cell count were at their highest on June 25, 1941.

One of us (L. A. S.) first studied her heart in detail on June 11, 1943. She was in the hospital for a blood transfusions and was as free of cardiac symptoms as she had ever been. All the previous clinical findings were verified. An orthodiagram and roentgenogram (fig. 1) revealed a huge cardiac silhouette compatible with the clinical findings. The electrocardiogram revealed sinus tachycardia. There was no evidence of increased venous pressure in the neck veins. Lung fields were clear. A diagnosis of huge cardiac enlargement as seen in severe anemia was made.

In the last admission to the hospital the girl appeared moribund. The cardiac findings were similar to those observed during previous admissions, but the presence of severe orthopnea with distended neck veins made one of us (L. A. S.) consider cardiac tamponade. The verbal report on the roentgenogram of the chest was that of massive cardiac enlargement. After discussion with the radiologist it was decided that nothing in the silhouette was incompatible with the diagnosis of pericardial effusion. A pericardial tap was done and about 50 cc. of blood-tinged fluid were obtained, but further drainage was stopped because it was thought that the blood-tinged fluid indicated that the cavity of the heart had been entered. She died the following day.

It was, therefore, no surprise to us that necropsy revealed a massive pericardial effusion, but we were amazed to learn that the heart was essentially normal in size.

The necropsy was performed by Dr. E. E. Aegerter, professor of pathology at Temple University Medical School, and the diagnosis was erythroblastic anemia with marked hemosiderosis of all organs. The following description of the heart is abstracted from Dr. Aegerter's report:

Heart: The pericardial sac was tremendously distended. It measured 19 cm. from its prominent right border to the apex and contained 44 oz. of bloody fluid. The fluid was thinner than normal blood. When centrifuged, the cellular content made up only approximately 15 per cent of the volume, indicating that the fluid was an effusion with blood contamination. Both layers of the pericardium were covered by a fibrinous exudate. The heart was about normal size. It weighed 300 grams. The epicardium was considerably thickened. The myocardium was pale, giving the gross appearance of a fatty degeneration. The coronary arteries were normal. There were no abnormalities nor evidences of inflammation on the valves.

Microscopic examination of the heart revealed fatty degeneration of the myocardium, hemosiderosis and chronic fibrosing pericarditis (fig. 2). Cultures of the pericardial fluid were sterile.

Case 2: S. C., a female, age 74, was admitted into Temple University Hospital October 15, 1948 and discharged November 27, 1948. When 59, she was told she had pernicious anemia. She was given liver extract that induced a remission. For two years her daughter had given her injections of liver extract, dilute rather than concentrated. In spite of this, she remained entirely free of symptoms until the day of admission, when she fell down three steps and injured her left shoulder.

Physical examination revealed an extremely pale but well-nourished woman in no obvious distress. The heart appeared normal in size and was normal on auscultation. There was slight tenderness in the left shoulder. A roentgenogram revealed an incomplete crack in the left humerus which required no specific treatment except rest.

The blood count was characteristic of pernicious anemia in relapse. There were 4.2 Gm. of hemo-

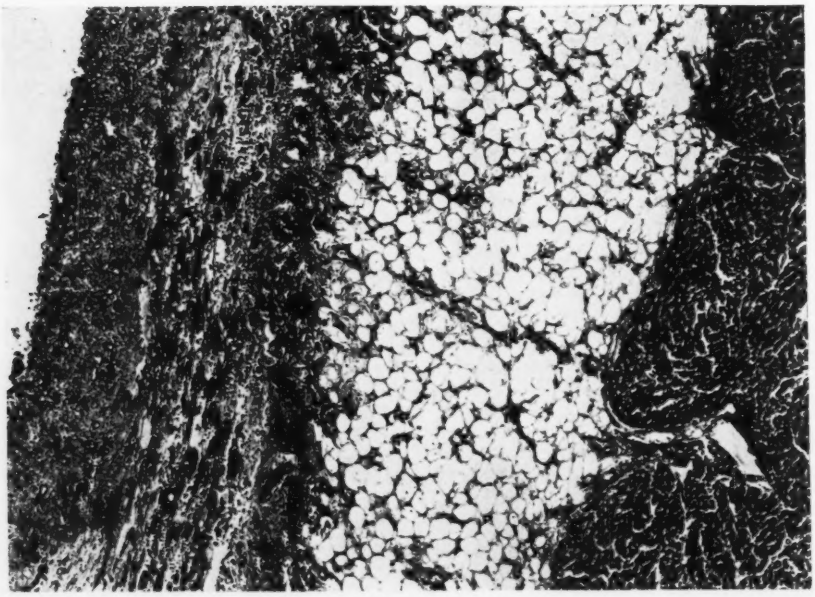

FIG. 2. L. L. Section of heart showing myocardium, increased adipose tissue and pericardial reaction.

FIG. 3. S. C. Roentgenogram showing enlargement of the so-called cardiac silhouette.

FIG. 4. S. C. Same as figure 3 after removal of 150 cc. of pale amber fluid that was replaced with 300 cc. of air. Note the size of the intrapericardial aorta and the cardiac silhouette visible above the fluid level.

globin and 890,000 red blood cells per cu. millimeter. The mean corpuscular hemoglobin was 47, the mean corpuscular volume was 146. The reticulocytes were 3.4 per cent, the hematocrit 13 and the blood smear showed macrocytosis. The bone marrow was megaloblastic. The gastric juice was free of acid and the gastrointestinal tract was normal by x-ray examination. The patient was given refined liver extract. At the time of discharge, an examination of her blood showed 12 Gm. hemoglobin, 3,850,000 red blood cells and a mean corpuscular volume of 98. Her family was instructed to use refined liver extract in sufficient dosage. It is important to note that at no time did she have any symptoms referable to the cardiovascular system.

When she was last seen in the out patient department the blood count was entirely normal.

The Heart: A roentgenogram of the chest revealed incidentally partial collapse of the ninth thoracic vertebra due to osteoporosis. The lung fields were clear. The heart was reported as being moderately enlarged in all its diameters (fig. 3). The electrocardiogram showed sinus tachycardia and left axis deviation. The voltage was within normal limits but appeared comparatively low for this type of body build and heart.

Based upon our experience with the first case and upon our experience with the heart in myxedema,[4] we felt incapable of excluding pericardial effusion as a cause for the enlargement of the so-called cardiac silhouette. We therefore decided to do a diagnostic pericardial tap. We were rewarded by our ability to remove very easily 150 cc. of pale amber fluid which we replaced with 300 cc. of air. (fig. 4.)

FIG. 5. S. C. Diminution in size of so-called cardiac silhouette after liver therapy.

The pericardial fluid contained 9 white blood cells per cubic millimeter. There was no growth on culture. The chemical composition of the fluid and the corresponding amounts of the blood examined on the same day were as follows:

	Pericardial Fluid	*Blood*
Protein	4.0 Gm.	6.5 Gm.
Albumen	2.9 Gm.	4.1 Gm.
Globulin	1.1 Gm.	2.4 Gm.
A/G	2.7	1.7
Cholesterol	40 mg.	140 mg.
Na	147 mg.	148 mg.
K	4.5 mg.	4.1 mg.
Chlorides	391 mg.	364 mg.
Mucin	negative	

Under no other therapy except that for the anemia, the effusion slowly disappeared and the cardiac silhouette diminished in size (fig. 5.)

COMMENT

These two cases illustrate the fact that pericardial effusion may be one cause for enlargement of the so-called cardiac silhouette in anemia as seen in the roentgen ray film. Furthermore, pericardial effusion may exist for years without producing symptoms or signs of tamponade. In our first patient, judged by the heart size at necropsy, pericardial effusion was present from her first admission into Temple University Hospital. This period represents four years. There is no way of determining how long previous to her first visit to our hospital the so-called cardiac silhouette had been enlarged. In our second patient the pericardial effusion was at no time associated with cardiac symptoms. This patient would have been regarded as a typical example of cardiac dilatation responding to therapy for anemia had not a pericardial tap been done.

It is obvious, therefore, that neither the clinical findings nor, indeed, the roentgen findings, as determined by ordinary technic, can help us at all times in distinguishing cardiac dilatation from pericardial effusion. The electrocardiographic findings obviously are not crucial. It appears likely that visualization of the cardiac chambers by Diodrast may furnish the answer to this problem in differential diagnosis. The literature on the experimental production of anemia and on the anatomic findings in anemia was reviewed in an attempt to determine how often pericardial effusion occurred as the sole or major factor in enlargement of the so-called cardiac silhouette.

Experimental production of anemia produced by bleeding[5] has resulted in hypertrophy of the heart. The heart may double in weight if a very severe anemia is produced. The experiments upon which these conclusions are based were relatively acute ones. The possible readjustments that may occur during a slowly produced anemia have not been described. We were unable to find any reference to experimental work on enlargement of the heart with return to normal size after correction of the anemia.

Anatomic studies on untreated severe pernicious anemia will probably no longer be made except under very rare circumstances because of the excellent therapy available now for the disease. There are several anatomic reports in the pre-liver era. Cabot and Richardson[6] reported an increase in weight of the heart in 18 of 19 instances of pernicious anemia. Only five hearts weighed more than 400 Gm. They stated that three had other possible causes for enlargement. The protocol shows five others with associated disease such as coronary artery disease or "acute" or "subacute" glomerulitis. Three hearts weighed only 285 Gm., 267 Gm., and 262 Gm., respectively. Reid[7] later examined the hearts of 11 individuals who had pernicious anemia and found that enlargement of a degree recognizable clinically was not found. Six weighed between 200 and 300 Gm. and 5 between 300 and 400 Gm. Unfortunately the presence or absence of pericardial effusion is not mentioned. In individuals who died of congestive failure apparently secondary to pernicious anemia, serous effusions, including pericardial effusion, were present.

As far as erythroblastic anemia is concerned, we are indebted to the excellent and thorough anatomic study of Whipple and Bradford.[8] They were primarily interested in the pigment abnormalities in this disease and did not comment specifically on pericardial effusion, but unlike so many other reports their anatomic descriptions are thorough and give specific information on the topic we are discussing. These authors stated that the heart in erythroblastic anemia may be enlarged and that serous effusions are common. They reported 3 cases, in all of which lemon-yellow hydropericardium was present.

A clinical diagnosis of cardiac enlargement was made in each instance but at necropsy only one heart was enlarged. The hearts weighed 71 Gm., 160 Gm., and 270 Gm. The pericardial cavities contained respectively 80 cc. of fluid, "a considerable excess of fluid," and 450 cc. of fluid. There is therefore more than a possibility that, in the presence of roentgenologic evidence of enlargement of the so-called cardiac silhouette in erythroblastic anemia, pericardial effusion may be a contributory factor in the enlargement of the roentgen ray shadow.

It is interesting to note that Whipple commented on the similarity of the bone marrow changes of erythroblastic anemia to those of pernicious anemia and to the similarity of the pigment changes of erythroblastic anemia to that of hemochromatosis. It is perhaps noteworthy that heart failure is a complication of hemochromatosis. This failure has been attributed both to disturbance in contraction of the myocardium because of the excessive pigment deposition and also to endocrine disturbances secondary to similar pigment deposits in the endocrine glands. But pericardial effusion has been reported as an incidental finding in hemochromatosis with and without heart failure. Chesner[9] reported an instance of hemochromatosis with apparent clinical enlargement of the heart. Clinically the heart extended from the anterior axillary line to a point more than two fingers breadth to the right of the sternum, yet the heart at necropsy was grossly normal and weighed 250 Gm. This discrepancy is not explained in the necropsy protocol. It would appear that interest was so centered on the problem of hemochromatosis that the pericardial effusion was not described.

The cause of the occasional presence of pericardial effusion in these blood dyscrasias is not clear. It may be that excessive pigment deposits in the pericardial membranes act as irritants to produce effusion. In support of this concept is the report of a case by Dubus[10] who describes the anatomic findings in a man of 66 years who died in heart failure. Anatomic examination revealed a massive pericardial effusion of 1500 cc. The fluid was sanguinous. Microscopic examination revealed fibro-adipose thickening of the visceral epicardium with excessive blood pigment deposition. No other cause for the pericardial effusion was discovered. Dubus called this lesion hemopigmentary pericarditis with effusion.

It is also possible that in anemia there may be a redistribution of fluid within the functional compartments of body water as Sokalchuk, Bello and Soloff found in myxedema.[11] In the latter disease, the interstitial fluid, including

the pericardial fluid, is increased and the blood volume is decreased. Under thyroid therapy, the blood volume increases and the interstitial fluid, including the pericardial fluid, decreases. In anemia, the blood volume is reduced and there is a well-known tendency to formation of edema. There does appear to be a general relationship, other things being equal, between blood volume and cardiac size. This is most clearly seen in diseased states with rapidly changing blood volumes. In addisonian crisis, for instance, the cardiac silhouette is extremely small and the blood volume is sharply reduced. With the exhibition of desoxycorticosterone acetate, there is a rapid increase in blood volume and cardiac size. But if excessive amounts of this drug are used, fluid accumulations appear in the serous cavities and in the subcutaneous tissue. The further increase in size of the so-called cardiac silhouette can very well be due to fluid accumulations within the pericardial sac. There is persuasive indirect evidence for this assumption but we did not feel it safe to tap the pericardium of a patient who exhibited the phenomena of overdosage with this drug. A similar train of events may possibly occur in anemia. The heart in anemia dilates, but at some critical point, which may vary in different types of anemia and from patient to patient, fluid accumulations occur. The pericardial effusion may simply be more easily detectable than accumulations of fluid elsewhere, or, once present, its reabsorption may be difficult.

Finally, these two cases may be rare exceptions to the usual course of events in anemia.

Conclusions

1. A case of erythroblastic anemia of Cooley and one of pernicious anemia are reported in which massive pericardial effusions were present and were mistaken clinically and roentgenologically for cardiac enlargement.

2. The possible causes of these effusions are discussed.

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Lodging of an Embolus in a Patent Foramen Ovale

By FABIAN J. ROBINSON, M.D.

A 77 year old man developed severe chest pain and collapsed seven days after prostatectomy and died three days later. Necropsy revealed thrombosis of right femoral vein, complete embolic obstruction of the primary branches of the pulmonary artery, and an embolus, 10 cm. long and 0.5 cm. in diameter, lodged in the foramen ovale. Although no systemic arterial emboli were found, it can be readily seen how such emboli could have developed.

THE RELEASE of a venous thrombus into the circulating blood and its paradoxical passage through a patent foramen ovale to produce systemic arterial embolism is a well known clinical and pathologic entity.[1] However, the actual anatomic demonstration of an embolus lodged in a patent foramen ovale is an infrequent observation at autopsy as judged by the finding of only fourteen cases reported in the world's literature.[2–12]

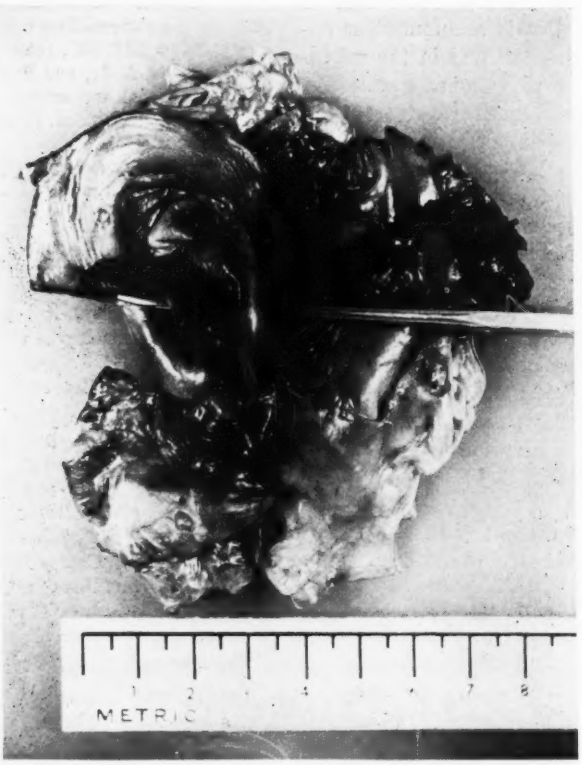

FIG. 1. The foramen ovale is patent and an embolus is impacted in it.

To illustrate again the intracardiac morphologic basis for paradoxical embolism, the following case is reported.

From the Department of Pathology, Parkland Hospital, Dallas, Texas.

Case Report

N. H., a 77 year old Negro man entered Parkland Hospital on August 3, 1948, with a complaint of urinary retention of one week's duration. A diagnosis of benign prostatic hypertrophy was made, and a suprapubic prostatectomy was performed seven days after admission. The patient's postoperative course was uneventful for seven days. On the eighth day after operation the patient suddenly collapsed, "broke out in a cold sweat," and became pulseless. One-half hour later he complained of a "feeling of pressure" in the substernal region that did not radiate. At that time the pulse was 100 per minute and regular and the blood pressure was 100/60. Two hours after the original episode, the patient experienced a second attack of chest pain, this time with radiation down the left arm. He gave no previous history of chest pain, cardiovascular symptoms, or tenderness and swelling of his legs. He expired three days after his original attack of chest pain.

At autopsy the following pertinent observations were made: (1) thrombosis of right femoral vein; (2) embolus, 10 cm. in length and 0.5 cm. in diameter, impacted in the foramen ovale (fig. 1); (3) complete obstruction of the primary branches of the pulmonary artery by emboli; (4) two small, peripheral, wedge-shaped pulmonary infarcts, one in the base of the right and one in the base of the left lung; (5) absence of demonstrable systemic arterial emboli.

The portion of the embolus in the left auricle, which is by definition a paradoxical embolus, could have given rise to systemic arterial emboli, although none were found.

Summary

The pathogenesis of paradoxical embolism is briefly stated, and a case is reported which illustrates the premise of intracardiac linking between venous thrombosis and paradoxical systemic arterial embolism.

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ABSTRACTS

BLOOD COAGULATION

Powers, J. S., Jr.: Toxicity of Dicumarol: Review of the Literature and Report of Two Cases. Ann. Int. Med. **32:** 146 (Jan.), 1950.

The author reports two cases of chronic congestive failure in which dicumarol resulted in severe hemorrhage. One patient died. Slight icterus was present prior to hemorrhage in one case and after hemorrhage had begun in the other. It is believed that chronic passive congestion of the liver interfered with the function of prothrombin formation to such an extent that administration of what had previously been safe doses of dicumarol so severely disrupted the clotting mechanism as to cause hemorrhage. Diminished renal filtration due to congestive failure may also have caused retention of dicumarol to such an extent that toxic levels were reached following administration of doses which ordinarily would not be expected to result in excessive acceleration of prothrombin time. For this reason, it seems justifiable to use extreme caution in the future when administering or planning to administer dicumarol to patients in chronic congestive heart failure.

WENDKOS

CONGENITAL ANOMALIES

Hamilton, W. F., Winslow, J. A., and Hamilton, W. F., Jr.: Notes on a Case of Congenital Heart Disease with Cyanotic Episodes. J. Clin. Investigation **29:** 20 (Jan.), 1950.

The authors report the case of an 18 year old Negro girl with congenital heart disease who suddenly became cyanotic, lost consciousness and had other signs of cardiorespiratory difficulty. Cardiac catheterization was performed and during the procedure the patient became very cyanotic and restless. It was found that the oxygen saturation of blood from the right auricle, the right ventricle and the femoral artery was the same (19%). The femoral arterial pressure was 80/40. The right ventricular pressure was high (100/0) while the pressure in the pulmonary artery was very low (5/0). The catheter could also be introduced into the aorta and carotid artery, indicating the presence of an interventricular septal defect. Oxygen consumption studies indicated that when the patient became cyanotic the oxygen consumption diminished markedly; this was associated with a fall in blood pressure from a normal of about 165/110 to levels as low at times as 65/30. These data were felt to be compatible with the diagnosis of tetralogy of Fallot.

The authors believe that these bouts of cyanosis were due to the relative resistances in the pulmonary and systemic beds. With a marked degree of pulmonary stenosis, very little blood is forced into the pulmonary circuit, but with a marked decrease in peripheral arterial resistance in the presence of a patent interventricular septum, most of the blood is diverted into the low pressure aorta and little or none is then pushed into the pulmonary circuit. It is suggested that the squatting position that many children with cyanotic heart disease learn to assume improves the venous return and increases the systemic resistance by pressure on the great abdominal and leg arteries.

BUTTERWORTH

Josephs, H. W.: The Mechanism of the Reduction of Red Cells and Hemoglobin following Operation for the Tetralogy of Fallot. Bull. Johns Hopkins Hosp. **86:** 1 (Jan.), 1950.

Twenty cases of the tetralogy of Fallot were studied to determine the mechanism of red blood cell and hemoglobin reduction following operation. The reticulocyte percentage, which was above normal prior to operation, decreased markedly after operation, indicating a decided diminution in erythrocyte formation. The marked drop in reticulocytes corresponded within a few days to the six-day period required for a reticulocyte to "mature" or to lose its reticular substance. Therefore, it is evident that decreased blood formation occurs practically immediately after operation. The duration of the diminution of hemopoiesis, however, was not determined.

Before operation the urobilin excretion was found to be 2 to 6 times greater than normal. This rate of destruction was greater than could be accounted for by the increase in hemoglobin mass. It is therefore believed that this abnormal increase in urobilin was caused by a shortening of the life span of the erythrocyte. Following operation the urobilin excretion was markedly increased, in many cases as high as one would expect in a severe hemolytic anemia, for approximately one week and then rapidly fell to normal. This was indicative of marked erythrocyte destruction.

The author concludes that the decrease in red blood cells and hemoglobin following operation is due to the destruction and lack of formation of

erythrocytes. The author's calculation of the ratio between the total urobilin excretion and the fall in hemoglobin indicates that the major factor is blood destruction. The similarity between the red cell reduction in these cases and the reduction in hemoglobin and red cells in the newborn is pointed out. The author postulates that blood destruction in these cases is the result of a controlled physiologic process, having as its "purpose" the reduction in the number of red blood cells.

MARGOLIES

Morgan, E. H., and Burchell, H. B.: Ventricular Septal Defect Simulating Patent Ductus Arteriosus. Proc. Staff Meet., Mayo Clin. **25:** 69 (Feb.), 1950.

This report deals with a patient who had the clinical manifestations of patent ductus arteriosus. After cardiac catheterization, however, the diagnosis of patent ductus arteriosus was no longer tenable, and thoracotomy for ligation of a patent ductus arteriosus was not advised. There are a number of congenital cardiac anomalies in which clinical findings characteristic of patent ductus arteriosus have been observed. In the patient herein described the presence of a ventricular septal defect was demonstrated by cardiac catheterization. If the patient had been considered to have aortic insufficiency also, it would have explained the diastolic murmur and the findings of low diastolic blood pressure.

Although rare, congenital defects in the aortic septum, either above or within the right aortic sinus, communicating with pulmonary artery or right ventricle, may produce clinical signs similar to those of patent ductus arteriosus. It is conceivable that the distinction of such defects from patent ductus arteriosus could be difficult, even with the aid of cardiac catheterization. An arteriovenous aneurysm on the pulmonary artery giving the typical clinical picture of a patent ductus arteriosus has been reported.

SIMON

Epstein, B. S.: Angiocardiography: Its Application to the Diagnosis of Coarctation of the Aorta. Radiology **54:** 211 (Feb.), 1950.

The author presents three cases of coarctation of the aorta with hypertension in the upper extremities and hypotension or absence of pressure readings in the popliteal spaces. Angiocardiography demonstrated not only the site of the coarctation and the individual dilated arteries central to this site, but also the collateral circulation. The descending aorta was visualized also.

There were no rib erosions in two of the patients, aged 13 and 14 years, respectively. Their intercostal arteries did not extend to the rib margins. The author believes that increased intercostal flow rather than increased pressure accounts for their tortuosity, along with the factor of time during which the arteries can approximate the inferior rib margins to erode them.

SCHWEDEL

CONGESTIVE HEART FAILURE

Fiese, M. J., and Thayer, J. M.: Value of Southey-Leech Tubes in Rapid Relief of Massive Edema. Arch. Int. Med. **85:** 132 (Jan.), 1950.

The authors state that the mechanical removal of edema fluid from the soft tissues is a valuable and physiologically sound therapeutic procedure. The Leech modification of the Southey tube is superior to the original model. These tubes, although rapidly drawing off large amounts of fluid, remove salt in only physiologic concentration, thereby avoiding the serious depletion of sodium which may accompany other methods. The prophylactic use of penicillin has abolished the risk of serious infections which in the past sometimes followed the mechanical removal of edema fluid. The definite indication for the use of Southey-Leech tubes is the presence of massive, soft, pitting edema, whether in the nephrotic syndrome, congestive heart failure or other diseases, which has failed to respond to the usual therapeutic measures. A relative indication for the use of these tubes is the presence of edema from which rapid relief is desirable and in which mechanical methods may supplement and potentiate the therapy ordinarily used. Their use is contraindicated in infected, hard or brawny edema.

BERNSTEIN

James, A. H.: The Mechanism of Pleural and Ascitic Effusions, with a Suggested Method for the Indirect Estimation of Portal Venous Pressure. Clin. Sc. **8:** 291, 1949.

An attempt was made to study the mechanisms of the production of effusions by measuring the various forces involved. Venous pressures were obtained at the antecubital space and effusion pressures were determined by means of a simple manometer. Protein estimations of blood and effusion samples were made, and from such data the colloid osmotic pressures of plasma and fluid were calculated.

In patients with pleural effusion, the venous pressure always exceeded the pleural pressure, the difference between the two being approximately equal to the difference between the colloid osmotic pressures of plasma and fluid. In the patients with ascites due to causes other than cirrhosis, the same relationship held. However, in the patients with cirrhosis, the ascitic pressure exceeded the venous pressure, while the difference between the colloid osmotic pressures was large because of the low protein content of the ascitic fluid. Such differences, as compared with the results obtained in other patients, were considered to be due to the portal obstruction that existed in cirrhosis. The magnitude of the de-

viation appeared to provide a measure of the portal pressure.

Since the albumin content of effusion fluid was proportional to that of plasma, while the globulin content was not, except in tuberculous pleurisy, the author concludes that albumin enters effusion fluid largely by simple diffusion, but that globulin only does so where capillary permeability is increased by inflammation.

ABRAMSON

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Liebow, I. M., and Hellerstein, H. K.: Cardiac Complications of Diabetes Mellitus. Am. J. Med. **7:** 660 (Nov.), 1949.

Coronary arteriosclerosis occurs more frequently and earlier in diabetics than in nondiabetics, and its occurrence is related to the duration of diabetes rather than to the severity of the metabolic disorder, the adequacy of control, the type of diet, or the age of the patient. There is an increased incidence of angina pectoris and coronary thrombosis in diabetics, the increase being particularly marked in women. Diabetics also manifest an increased incidence of hypertension and congestive heart failure.

Peripheral circulatory collapse is a prime feature of diabetic acidosis, and the mortality rate increases with the degree of systolic and diastolic hypotension. In the circulatory shock of diabetic acidosis there is dehydration, hemoconcentration, loss of sodium and chloride, and a marked decrease in total peripheral resistance; the cardiac output remains normal. Hypopotassemia, which occurs after the institution of treatment for diabetic acidosis and is manifested by characteristic changes in the electrocardiographic pattern and by abnormalities, in some cases, in the cardiac rhythm, may be the factor responsible for the death of some patients with diabetic acidosis, which terminates fatally despite therapeutic achievement of normal blood sugar and carbon dioxide combining power values.

Hypoglycemic reactions from too enthusiastic insulin administration in older diabetics may precipitate cardiac complications such as angina, myocardial infarction, congestive failure, and arrhythmias. These changes are probably mediated by an increased secretion of epinephrine secondary to the hypoglycemia. For this reason, rigid control of elderly diabetics is hazardous.

HANNO

Oram, S., and Holt, M. C.: Coronary Involvement in Dissecting Aneurysm. Brit. Heart J. **12:** 10 (Jan.), 1950.

The authors state that the coronary blood flow may be rendered inadequate in dissecting aneurysm (1) rarely by an extension of dissection into the coronary arteries, (2) by occlusion of their ostia, and (3) by compression of the vessels by hemopericardium or by infiltration with blood of the perivascular tissue. The authors report a case of the last type occurring in a man age 73. The necropsy revealed a dissecting aneurysm with hemopericardium. There was diffusion of blood along the wall of the left coronary artery and its anterior descending branch for a distance of 4.5 cm. from its orifice.

The authors state that the electrocardiographic findings are not those typical of infarction. When changes are present, they consist of elevation of the RS-T segment with T wave inversion in either Lead I or Lead III without the presence of Q waves.

SOLOFF

Pondé, Adriano A., and Pondé, Alberto, A.: The Use of Supplementary Thoracic Leads in the Diagnosis of Mycardial Infarction. Arq. brasil. cardiol. **3:** 1 (March), 1950.

In certain cases of myocardial infarction the usual precordial leads do not show the characteristic QRS changes and may even be of normal configuration The use of additional thoracic leads at higher levels of the precordium are of great value in demonstrating the presence of high anterolateral and basal infarcts. It is suggested, therefore, that high precordial leads should be recorded in all cases in which a positive clinical history for coronary occlusion is obtained in the absence of diagnostic changes in the usual leads.

The authors report five cases which demonstrate the value of supplementary thoracic leads in the electrocardiographic diagnosis of high anterolateral and high anteroseptal infarctions.

SCHLESINGER

ELECTROCARDIOGRAPHY

Simonson, Ernest, and Keys, Ancel.: Experimental Malaria in Man. III. The Changes in the Electrocardiogram. J. Clin. Investigation **29:** 68 (Jan.), 1950.

To study the effect of malaria on the normal heart, the authors recorded three standard limb leads both in the supine position and at a tilt angle of 68 degrees on 12 normal young men both before and on two occasions after the termination of experimental blood-induced vivax malaria. The duration of P, QRS, P-R, and Q-T were measured as were the amplitudes in each lead of P, QRS, and T. The sums of the QRS, T and S-T segments as well as the QRS and T axes were also determined. Mechanical systole was estimated by the interval between the first and second tones in a simultaneously recorded stethogram.

Analysis of the results indicated that 12 of the 14 items measured were significantly changed after malaria, including a general tendency to depression of T and the S-T segment in Leads II and III, and, in the upright position, a large shift of the T-axis to the left. The tilt table was found useful in re-

vealing changes not present in the supine position. The authors note, however, that although most of the changes were statistically highly significant, they occurred within the so-called range of normal limits.

BUTTERWORTH

Kossman, C. E.: Unipolar Electrocardiography, Including Intracardial Leads, in the Diagnosis of Myocardial Disease. Bull. New York Acad. Med. **26:** 20 (Jan.), 1950.

The author compares the Wilson electrode (central terminus "T") with the Goldberger augmented leads. Because the latter do not use resistors in series with each extremity they are considered to be an unacceptable technique in unipolar electrocardiography. The "bipolar technique" of Cohen and Glicksman (W_R, W_L, W_F) gives a reasonable approximation of the extremity potential (Wilson) but of about twice the size. One electrode is placed on the extremity to be studied and the other on the body at a point as diametrically opposite as possible. Esophageal leads are useful in the study of the electrophysiologic behavior of the left atrium. The precordial patterns of electrical (and anatomic) rotation of the heart as well as of myocardial infarction are discussed.

Intracardiac leads indicate that the Q wave in the bipolar leads has its origin in the left side of the interventricular septum and the R wave in the apical portion of the left ventricle. The S wave in precordial leads, or at least a major part of it, is believed to arise in a mass of muscle at the base of the right ventricle.

Methods of the future include (a) plotting null-potentials of the QRS complex on the chest, (b) vectorcardiography and (c) the radarscope which records potential differences as differences in brightness of the image.

WHITE

HYPERTENSION

Kappert, A. von: The Management of Hypertension with Dihydrogenated Ergot Alkaloids. Helvet. med. acta, **16:** 127 (Sup. 22), 1949.

Hydergine (CCK 179), the combination of the three dihydrogenated ergot alkaloids of the dimethylpyruvic acid group, has been shown to be the most active and best tolerated of the drugs investigated in the treatment of various forms of high blood pressure, such as juvenile hypertension, high blood pressure with subjective symptoms in the absence of organic damage, hypertension with prominent cerebral, retinal, renal or myocardial (electrocardiographic changes, angina pectoris) damage, and hypertension with hormonal disturbances or with peripheral vascular disorders. Hydergine has proved clearly superior to bromides, barbiturates, purine derivatives, etc. Objectively its therapeutic action is manifested by a reduction of the systolic and the diastolic blood pressures, improvement of the alterations of the optic fundus caused by hypertension, and improvement of the electrocardiogram and of disturbed renal function. In addition, a favorable influence is obtained on the subjective symptoms of hypertension, including headache, vertigo, tinnitus, fatigue, sleeplessness, blurred vision, scotoma, hot flushes, ataxia, and tremor.

In patients with mental symptoms oral treatment with gradually increasing doses usually suffices. Generally improvement is seen after twelve days of treatment and a full therapeutic effect after twenty to thirty days; the combined oral and parenteral treatment with Hydergine, however, is considerably more effective with improvement being evident after only seven days and a full therapeutic action after sixteen days. The combined treatment is especially recommended for severe cases. Either method however, requires single or repeated courses of treatment of 2 to 3 months interrupted by intervals free of medication or permanent treatment. Medication should not be abruptly discontinued but gradually reduced, in oral therapy, by a daily reduction of one to two drops with each dose.

AUTHOR

Chapman, C. B., and Gibbons, T. B.: The Diet and Hypertension. A Review. Medicine **29:** 29 (Feb.), 1950.

The authors review the historical background and the modern development of attempts to affect hypertension in man by dietary means. The reported results are critically evaluated.

Increased salt intake may cause a rise in blood pressure in some cases of pre-eclampsia, and probably also in some cases of renal and essential hypertension. On the other hand, restriction of salt has not been conclusively shown to reduce the blood pressure of hypertensive patients independently of other factors. Certain diets such as those proposed by Allen, and particularly Kempner, cause a significant reduction in blood pressure in some patients. Adequate control studies indicate that such reduction cannot be explained by spontaneous fluctuations of pressure levels. However, the possibility that suggestion may play a part has not been ruled out.

There is no convincing evidence that fat and cholesterol play an important role in the cause of hypertension, or that their restriction favorably affects the course of hypertension. Protein intake reduction has not been shown to lower blood pressure in hypertension. Obesity is associated with increased incidence of hypertension, and weight reduction often results in a fall in pressure (chiefly systolic). Starvation tends to lower blood pressure in normotensive as well as hypertensive persons. The effect is quickly reversible. Other dietary factors such as carbohydrate, vitamins, caffeine, alcohol, watermelon seed, and garlic—whether fed in quantity or withheld—have not been shown to have

therapeutic value. "It is indeed unfortunate that fantastic and virtually unsupported claims, which have been irresponsibly introduced into the literature, can be disproved only by means of time-consuming and expensive techniques."

ENSELBERG

Bowen, G. L., Grandin, D. J., Julien, E. E., and Krech, S., Jr.: Pheochromocytoma Complicating Pregnancy. Am. J. Obst. & Gynec., **59**: 378 (Feb.), 1950.

This is the sixth reported case of pheochromocytoma associated with pregnancy. A 26 year old primigravida at term complained of headache, mild generalized edema, and slight albuminuria. In the first stage of labor the blood pressure fluctuated around 150/100. A stillbirth was delivered by low-forceps. After delivery of the placenta ergotrate was administered. The blood pressure rose to 210/120 and the patient became cyanotic. In five minutes, following morphine, intravenous magnesium sulphate and hypertonic glucose, the pressure fell to 110/60. The pressure continued to fluctuate widely but was unobtainable ten hours post partum. Acute fatal left ventricular failure occurred six hours later. A pheochromocytoma, weighing 100 Gm. and containing about 1 mg. of epinephrine per cc. of tumor fluid, was found at autopsy. The similarity of the syndrome produced by such a tumor and that produced by toxemia of pregnancy is discussed.

WAIFE

PATHOLOGIC PHYSIOLOGY

Stone, P. W., and Murphy, R. A., Jr.: A Method for Experimental Production of Gradual Occlusion of the Portal Vein. Proc. Soc. Exper. Biol. & Med. **72**: 255 (Oct.), 1949.

A sudden complete occlusion of the portal vein is invariably fatal. The proximity of the portal vein to the pancreas and its occasional invasion by pancreatic carcinoma in man have led many to investigate methods for the production of adequate collateral channels, thereby enabling excision of this vessel.

The present study is a report of the use of irritative cellophane (Polythene) and tantalum to produce gradual portal vein occlusion. The portal vein in 28 dogs was wrapped with Polythene and partially occluded with tantalum. Four dogs died within twelve hours because of too sudden occlusion. The remaining 24 dogs showed no ill effects from the procedure. The portal vein was excised from 16 dogs without a fatality at intervals ranging from five to sixty days.

At the time of excision of the portal vein, extensive collateral venous channels were present in the gastrohepatic mesentery. No elevation of the venous pressure was found in the intestinal veins. Significant anastomoses with the esophageal veins were not demonstrated. This is of interest when compared with the usual collateral channels found in man following obstruction of the portal vein. The degree of fibroplasia of the portal vein was dependent upon the duration of Polythene application. The lumen of the portal vein was completely occluded after forty to sixty days.

The authors conclude that the gradual occlusion of the portal vein by irritative Polythene may be valuable in preparing for elective ligation of the portal vein and in the experimental study of decreased portal blood flow.

MINTZ

Rosenfeld, L., Langohr, J. L., Owens, C. R., and Cope, O.: Circulation of the Blood and Lymph in Frostbite and Influence of Therapeutic Cold and Warmth: An Experimental Study. Arch. Surg. **59**: 1045 (Nov.), 1949.

The effect of cold and warmth in counteracting the changes produced by experimentally induced frostbite was studied in dogs. The alterations in circulation produced by immersing the dog's foot in a liquid mixture of ethyl alcohol and solid carbon dioxide consisted of a decrease in blood flow in proportion to the severity of injury and then an increase when thawing began. During the latter stage there was also an increase in lymph flow and protein concentration of the lymph comparable to that following a burn. Both cold (10° C.) and warmth (40° C.) had very little effect on the abnormal changes in blood flow produced by frostbite. However, cold appeared to retard the abnormal lymph flow, the lymph protein concentration, and the edema formation. Warmth appeared to have very little beneficial effect as therapy in frostbite.

ABRAMSON

Albrink, M. J.: The Choline-Containing Phospholipids of Serum. J. Clin. Investigation **29**: 46 (Jan.), 1950.

Because of the established role of choline as a lipotropic factor, the authors investigated the level of lipotropic substances in the serum to see if this level was a contributing factor in human liver disease. In 23 normals, 27 patients with diseases of the liver or biliary tract and 12 patients with other diseases, the lipid phosphorus and choline contents of the serum as well as the free and total cholesterol and fatty acid contents were determined. In the 23 normal subjects the lipid phosphorus varied from 2.16 to 3.78 millimoles per liter with an average of 2.83. The ratio of moles choline to moles phosphorus varied from 0.70 to 0.80 and seemed quite constant in one individual in whom multiple determinations were made. In the patients with liver disease, the ratio of choline-containing to total phospholipids was also found to be constant regardless of the concentrations of the total phospholipids or of the other lipid fractions.

The authors conclude that any abnormality in phospholipid metabolism will manifest itself as a change in the total lipid phosphorus rather than by changes within the phospholipid fractions.

BUTTERWORTH

Eaton, R. M.: Pulmonary Edema. Experimental Observations on Dogs Following Acute Peripheral Blood Loss. Dis. Chest **17:** 95 (Jan.), 1950.

The author presents a series of observations on dogs which show that acute peripheral blood loss will produce a marked degree of pulmonary edema and pulmonary hemorrhage. The pulmonary changes which follow bleeding were observed for as long as four or five days. It seems probable that following acute blood loss with a decrease in cardiac output, loss of blood volume, rapid fall in vascular pressure, and slowing of the circulation, there is a sudden state of circulatory anoxia. As a result of this anoxic state, capillary endothelium is damaged and becomes more permeable, and fluid from the vascular bed transudes into the tissue spaces and into the alveoli. A pulmonary block to normal circulation is produced as pulmonary congestion and edema become more severe and the pulmonary artery pressure and peripheral venous pressure rise.

The acute pulmonary edema of the first twenty minutes following blood loss may be due to two additional factors. These are the increased intra-alveolar negative pressure resulting from the deep breathing associated with blood loss and the increased intracapillary lateral pressure secondary to vascular congestion in the lungs. These dynamic factors are transient and there is a temporary flow of fluid from the tissues back to the vascular system. However, in one to one and one-half hours after blood loss a secondary rise of pulmonary moisture reaches its peak due to the gradual but sustained retransudation of fluid through the damaged endothelial structure and the increasing pulmonary artery pressure.

Intravenous fluid administration following blood loss may produce further damage to the pulmonary vascular bed by elevation of venous pressure and dilution of the plasma proteins. Greater degrees of pulmonary edema are noted when infusions of physiologic sodium chloride are given than when either plasma or blood is used. It is apparent that intravenous fluid administration should be given with caution to patients following acute blood loss.

SCHWARTZ

Olcott, C. T.: Experimental Argyrosis: Hypertrophy of the Left Ventricle of the Heart in Rats Ingesting Silver Salts. Arch. Path. **49:** 138 (Feb.), 1950.

The author reports the development of left ventricular hypertrophy in rats ingesting silver salts for prolonged periods. The animals imbibed solutions of silver salts in 1:1000 strength in place of drinking water. Each was bracketed with another, as control, using ordinary drinking water. The author comment on the difficulty of determining blood pressure in rats. After indecisive results while utilizing various procedures, the author relied on the weight of the left ventricle as an index of hypertension. Rats, silver treated, showed an increased weight of the left ventricle, which was not due to silver deposit in the heart muscle or to argyrosis anemia. The cause remains obscure. Heavy pigmentation of the basement membrane of the glomeruli was present and was possibly the cause of the hypertension and left ventricular hypertrophy.

GOULEY

Frankel, K.: Relation of Migraine to Cerebral Aneurysm, Arch. Neurol. & Phychiat. **63:** 195 (Feb.), 1950.

The author presents three patients with typical migraine, who subsequently developed intracranial aneurysm which was verified at operation or autopsy. A change in the type or location of headache occurred one to several months before the appearance of neurological signs which pointed to aneurysmal dilatation. There was a further change in the character of the headache at the time of massive dilatation and/or rupture of an aneurysm. These were associated with extraocular muscle palsies. It is conceivable that vascular factors present during a migraine headache (i. e. high intravascular pressure, stretching of relaxed cerebral vessels with systole) in a patient so predisposed may result in the formation of an aneurysm or dilatation of a minute aneurysm already present.

WAIFE

PATHOLOGY

Elkin, D. C.: Arteriovenous Aneurysm of the Phrenic Vessels. J.A.M.A. **141:** 531 (Oct. 22), 1949.

An arteriovenous fistula of the right phrenic vessels developed following repeated thoracenteses for a right pleural effusion. Clinically, the presence of the fistula was manifested by a harsh continuous bruit, accentuated in systole, over the right lower posterior chest wall. The lesion, the first of its kind to be reported, was successfully excised.

HANNO

Reynolds, R. P., Owen, C. I., and Cantor, M. O.: Arteriovenous Aneurysm of Uterine Artery and Vein. J.A.M.A. **141:** 841 (Nov. 19), 1949.

The authors describe a case of arteriovenous aneurysm of the uterine artery and vein (circoid aneurysm of the myometrium), the third such case to be reported. The disorder is characterized by softness of the uterus, which causes pregnancy to be suspected. Hysterectomy is indicated. In the case reported, dilatation of the cervix preparatory to diagnostic curettage precipated a frank hemorrhage and an emergency hysterectomy was per-

formed. Intra-abdominal hemorrhage occurred postoperatively and necessitated a second celiotomy. A bleeding vessel in the broad ligament was ligated and the patient made a good recovery.

HANNO

Langohr, J. L., Rosenfeld, L., Owen, C. R., and Cope, O.: Effect of Therapeutic Cold on the Circulation of Blood and Lymph in Thermal Burns: An Experimental Study. Arch. Surg. **59**: 1031 (Nov.), 1949.

The effect of cold on the abnormal circulation of blood and lymph and on the rate of edema formation induced by a thermal burn was studied in the feet of dogs. Under anesthesia, the lymphatic vessels of the hind limbs were cannulated and then the feet were burned, following which they were placed in a cold bath maintained at 10 C. It was found that exposure to cold altered the pattern of lymph flow and protein concentration. The rate of edema formation and therefore the rate of loss of plasma volume were diminished but not eliminated by this procedure.

It was concluded that although cold may retard the development of infection and diminish damage due to an impaired circulation, it also reduces the rate of the healing processes. Furthermore, an excessive use of cold may in itself result in tissue damage. On the basis of available evidence it would appear that cold should be limited to its use in producing temporary alleviation of the pain of burns of small extent.

ABRAMSON

Geiringer, E.: Venous Atheroma. Arch. Path. **48**: 410 (Nov.), 1949.

The author studied the lesion of venous atheroma, which, unlike phlebosclerosis and venofibrosis, is to be found in only one location, namely, at the junction of the left common iliac vein and the inferior vena cava, extending with each of these confluent veins for 1 or 2 cm. The same sequelae noted in arteriosclerosis, namely, hyalinization and calcification, were present in many cases. The plaque-bearing area was in that part of the vein which is situated entirely behind the aorta and the right common iliac artery. However, in one case of sinistroposition of the inferior vena cava, the venous bifurcation showed a sclerotic patch at the orifice of the right common iliac vein, i.e., where it was crossed by the left common iliac artery.

The implication is clear that regardless of the pathogenesis of atheromatosis, there is a fundamental mechanical factor—a pressure factor—which determines the site of atheroma. This venous atheroma is found regardless of the presence of congestive circulatory failure; the severity of aortic atheroma does not govern the degree of venous atheroma.

GOULEY

Schlichter, J., and Harris, R.: The Vascularization of the Aorta. II. A Comparative Study of the Aortic Vascularization of Several Species in Health and Disease. Am. J. M. Sc. **218**: 610 (Dec.), 1949.

By means of an injection technic, the vascularity of the ascending aorta in the dog, man, chicken, and rabbit was studied roentgenologically and microscopically. The vascularity was comparatively less for man, the chicken, and the rabbit, in that order.

From these data and other studies a general working hypothesis has been presented by the authors, namely, that the development of degenerative arterial lesions appears to vary inversely with the blood supply to the arterial wall. This hypothesis does not preclude the probability that other factors, such as hormones, intrinsic cellular metabolic defects, or heredity, may play a role in the evolution of these lesions, but it does emphasize the importance of the blood supply factor. Of the materials carried by the blood, oxygen would appear to be the most essential, for oxygen storage in tissue or tissue fluid is practically nonexistent. Conditions expected to produce degenerative arterial changes generally fall into two categories. In the first group are included those conditions which physiologically increase the demand for blood, and especially oxygen, by the arterial wall without proportional increase in the supply. Such a state of affairs might be found in hypertension or even in normal physiologic growth of the aorta. In the second group are conditions actually reducing blood flow, and thereby the oxygen supply, to the arterial wall. This state might be found in syphilitic aortitis where the vasa vasorum are destroyed or in clinical states causing prolonged anoxemia.

DURANT

PHARMACOLOGY

Clark, L. C., Jr., Gollan, F., and Gupta, V. B.: The Oxygenation of Blood by Gas Dispersion. Science **111**: 85 (Jan.), 1950.

A technic for the extrapulmonary administration of oxygen is described. Oxygen is dispersed in the blood in the form of tiny bubbles produced by passing the gas through a fritted disk or a porcelain bacteriological filter. The excess gas is released by passing blood over a surface coated with a methylpolysiloxane resin. Blood is removed from the heparinized dog through a catheter in the inferior vena cava and pumped through the mechanical device described. An oximeter, a glass cloth filter and a bubble trap are used in the apparatus. The oxygenated blood is returned through an external jugular vein.

Dogs breathing 100 per cent nitrogen showed none of the signs or symptoms of acute anoxic anoxia; oximetric readings were always over 95 per

cent saturation; and the blood pH remained constant during this oxygenation procedure.

WAIFE

Dewar, H. A., and Grimson, T. A.: Khellin in the Treatment of Angina of Effort. Brit. Heart J. **12:** 54 (Jan.), 1950.

In 12 subjects the authors compared the ability of Khellin and of glyceryl trinitrate to precent anginal pain and the electrocardiographic changes that sometimes accompanied it. Khellin prevented pain in 7, diminished it in 3 and had no effect in 2. Glyceryl trinitrate prevented pain in 10, increased it in one, and had no effect in one. Of nine electrocardiographic studies, glyceryl trinitrate prevented changes in two and decreased them in five. Khellin prevented change in one and decreased changes in three. Khellin appears less effective but its effects last longer than glyceryl trinitrate. The drug appears to warrant further study.

SOLOFF

Wechsler, R. L., Kleiss, L. M., and Kety, S. S.: The Effects of Intravenously Administered Aminophylline on Cerebral Circulation and Metabolism in Man. J. Clin. Investigation **29:** 28 (Jan.), 1950.

There is a widely held belief that aminophylline, in addition to its effect on bronchioles, kidneys and heart, also exerts a stimulating effect on central nervous function and improves the cerebral circulation. The authors investigated this theory by measuring the cerebral blood flow in 10 patients chosen at random without any obvious cerebral depression. The cerebral blood flow was measured by the nitrous oxide method, following which 0.5 Gm. of aminophylline in 250 cc. of physiologic saline solution was administered intravenously over a period of twenty minutes. As the last 50 cc. ran in, the cerebral blood flow was again measured. The cerebral oxygen consumption and the cerebrovascular resistance were also calculated.

It was found that aminophylline caused a significant decrease in cerebral blood flow; this appeared to be due to a highly significant increase in cerebrovascular resistance. The mechanism for the changes was not immediately apparent but it seemed probable that aminophylline constricted the cerebral vessels and thus caused the decrease in cerebral blood flow. It was noted that some patients reacted to the aminophylline with pronounced anxiety associated with disturbing symptoms and an increase in cerebral oxygen consumption.

BUTTERWORTH

Weiss, W. A.: Anesthesia in the Aging Group. Geriatrics **5:** 26 (Jan.–Feb.), 1950.

The choice of an anesthetic agent depends in part on the physiologic state of the cardiovascular system. Morphine may cause marked central depression, hypotension and respiratory depression resulting in cerebral anoxia. Demerol is preferred. It is better to supplement insufficient premedication than to anesthetize an over-premedicated patient. In elderly patients, cyclopropane is usually contraindicated because of impaired cardiac conduction. For light anesthesia, ether is a cardiovascular stimulant and tends to maintain blood pressure. Nitrous oxide and ethylene-oxygen mixtures might lead to suboxygenation and myocardial anoxia. Sodium pentothal should be given slowly in small repeated amounts to avoid respiratory depression. The prevention of anoxia is the basis of management in geriative patients. Sudden hypotension due to spinal anesthesia predisposes to coronary insufficiency so the use of vasopressor drugs is encouraged. Regional anesthesia has a wide application in elderly patients.

WAIFE

Forbes, G. B., Deisher, R. W., Perley, A. M., and Hartmann, A. F.: Effect of Hyaluronidase on the Subcutaneous Absorption of Electrolytes in Humans. Science **111:** 177 (Feb.), 1950.

By the use of sodium chloride containing radiosodium (Na_{24}) it was shown that in the normally hydrated subject the rate of absorption of the sodium ion from small volumes of subcutaneously injected fluid is enhanced by the addition of hyaluronidase.

SACHS

Goldman, J.: Effect of Cholesterol Feeding in Hamsters. Arch. Path. **49:** 169 (Feb.), 1950.

The author found that the hamster (Golden Syrian) recently recommended is unsuitable for the study of experimental cholesterol atheromatosis. Blood cholesterol was elevated by appropriate diet up to 342 mg. per cent over a period of sixty days without appreciable atheromatosis. Steatosis of the liver and testicular atrophy were noted in these animals.

GOULEY

White, S. M.: The Vasodilator—Roniacol. Minnesota Med. **33:** 133 (Feb.), 1950.

Roniacol, a 3-pyridine methanol, is an oral vasodilator which is converted to nicotinic acid in the body. With dosages of 100 mg. a marked flush is produced, particularly over the face and upper extremities, within six to twelve minutes. The effect is lessened if the stomach is not empty. The substance produces no significant change in pulse rate, respiratory rate or blood pressure. The author feels that the drug was of clinical value in 6 of 9 patients with angina pectoris, and in all of 3 patients with peripheral vascular disease, 2 with arteriosclerotic decubitus ulcers and 1 patient with Raynaud's disease.

WAIFE

PHYSICAL SIGNS

Parsonnet, A. E., Klosk, E., Bernstein, A.: Dysphagia in Cardiovascular Disease. J. Newark Beth Israel Hosp. **1:** 5, 1950.

Dysphagia caused by both congenital and acquired cardiovascular lesions is discussed and cases illustrating most of these conditions are presented. These cardiovascular causes of dysphagia (as well as intrinsic lesions of the esophagus, upper gastrointestinal tract and mediastinum) must be considered in the differential diagnosis of this syndrome. Such differential diagnosis is particularly important in the infant since some of these lesions are amenable to surgery. In the adult, it is important to consider cardiovascular disease, since dangerous endoscopic procedures may then be avoided. The importance of the barium swallow as part of routine cardiac fluoroscopy is therefore pointed up by these cases.

BERNSTEIN

PHYSIOLOGY

Lagerlof, H., and Werko, L.: Studies on the Circulation of Blood in Man. VI. The Pulmonary Capillsry Venous Pressure Pulse in Man. Scandinav. J. Clin. & Lab. Investigation **1:** 147 (No. 2), 1949.

After introducing a cardiac catheter deep enough into the pulmonary artery to obstruct one of its small branches, the authors recorded pressure tracings of the obstructed capillary area. The pulse tracing so obtained is called the pulmonary capillary venous (pcv) pressure pulse. Tracings were obtained from 50 subjects including normal persons, pregnant women, and patients with hypertension, mitral valve disease and pulmonary emphysema.

The mean pcv pressure was found to be approximately equal to the mean pulmonary venous pressure; it represents a somewhat distorted and slightly delayed pressure pulse of the small pulmonary veins. It was found to be about 2 mm. of mercury higher than the left auricular mean pressure in a compensated patient with atrial defect. The pcv mean pressure, and hence capillary pressure, in left ventricular failure was at times elevated above the osmotic pressure of the plasma. It could be decreased by the intravenous injection of aminophylline or Cedilanid. The authors discuss in detail the significance of the shape and amplitude of the pcv pressure pulse in the evaluation of mitral valvular function, in ventricular extrasystoles, in auricular fibrillation, in A-V block, and in gallop rhythm.

By superimposing the pcv and pulmonary artery pressures during the same period of respiration with due regard to the time lag, it was possible to get an approximate idea of the pressure difference between the pressures in the small pulmonary arteries and veins. The findings indicated that this pressure difference is greatest during systole and that the systolic flow through the pulmonary capillaries is greater than in diastole.

SCHWARTZ

Storstein, O.: Measurement of the Venous Pressure and of the Circulation Time. Acta med. Scandinav. **136:** 122 (Dec. 23), 1949.

A group of subjects consisting of 238 compensated and 178 uncompensated cardiacs, 28 hyperthyroids and 23 normal controls formed the material for this study. Circulation times were measured with Decholin and magnesium sulfate. The venous pressure was determined in the usual manner with the fourth intercostal space in the anterior axillary line taken as the zero point. Heart volume was measured by roentgenologic means. The circulation times were prolonged in left-sided heart failure, highest in right- and left-sided failure and normal in compensated and pure right-sided failure. The venous pressure was raised only in combined right- and left-sided failure. Heart volume was only slightly increased in left-sided failure, and was especially increased in combined heart failure.

The author's calculations failed to confirm Nylin's claim that the circulation time depends mainly on the size of the heart. It appears that congestion in the lungs is responsible for prolonged circulation times.

WAIFE

Huggins, R. A., Smith, E. L., and Sinclair, M. A.: Comparison between the Cardiac Input Measured with a Rotameter and Output Determined by the Direct Fick Method in Open-Chest Dogs. Am. J. Physiol. **160:** 183 (Jan.), 1950.

A sizable rotameter capable of measuring total venous return to the heart may be used to measure cardiac input. Repeated determinations in 8 dogs revealed an agreement between rotameter input and Fick principle output within plus or minus 10 per cent. Maximum differences were +25.8% and −26.6%.

HECHT

Peterson, L. H., Eather, K. F., and Dripps, R. D.: Postural Changes in the Circulation of Surgical Patients as Studied by a New Method for Recording the Arterial Blood Pressure and Pressure Pulse. Ann. Surg. **131:** 23 (Jan.), 1950.

By means of a small plastic catheter inserted intra-arterially and a capacitance manometer, the authors studied the blood pressure alterations produced by changes in posture in patients during a surgical procedure. They found that elevation of the leg may be more effective than pressor drugs in raising the blood pressure when hypotension results from a decreased peripheral resistance.

ABRAMSON

Spencer, F. C., Merrill, D. L., Powers, S. R., and Bing, R. J.: Coronary Blood Flow and Cardiac Oxygen Consumption in Unanesthetized Dogs. Am. J. Physiol. **160:** 149 (Jan.), 1950.

In fourteen trained and unanesthezised dogs the coronary sinus was catheterized, and a detailed study of cardiac work performance was made in 27 experiments by means of simultaneous measurements of cardiac output by the Fick principle. Ventricular blood flow was calculated by the nitrous oxide method of Kety and Schmidt. Since coronary sinus blood consists of blood which drains from the left ventricle, data concerning left ventricular functions only may be obtained by this method. Oxygen consumption of the left ventricle was estimated by the work equivalent of oxygen at a respiratory quotient of 0.82 (ml. oxygen/2.059 Kg. meters).

The oxygen content of coronary sinus blood ranged fron 2.2 to 7.3 vol. per cent with an average coronary arteriovenous difference of 12 vol. per cent. The average left ventricular oxygen consumption per 100 Gm. measured 15.75 ml./min. and left ventricular blood flow per 100 Gm. ranged from 79 to 220 ml./min. with an average of 133. The figures are dependent on left ventricular weight. Total ventricular flow was calculated to vary from 52 to 103 ml. per minute. Cardiac index varied from 2.8 to 6.7 liters, left ventricular work from 2.89 to 6.40 Kg./meters/min. Left ventricular efficiency was estimated at 30 per cent.

HECHT

ROENTGENOLOGY

Sutton, G. C., Wendel, G. E., Grant, H. E., and Warnick, E. G.: Circulation Times for Angiocardiography. Am. J. Roentgenol. **63:** 186 (Feb.), 1950.

The authors demonstrate an acceleration in the rate of flow when ether and sodium cyanide are dissolved in 50 cc. of saline rather than in the usual 5 cc. or less. This acceleration is attributed to increased rate of passage not only from the arm veins to the heart but apparently to the left ventricle also. Such determinations facilitate the accurate timing of exposures to be made in order to obtain satisfactory visualization of the left-sided heart chambers, a decrease in the number of serial exposures and lessened radiation effects. A table is presented in which the relationship of the circulation times is checked against the time of the visualization of the left chambers filled with the opaque dye. In 8 out of 10 normal patients the left ventricle and aorta were visualized within two seconds of the circulation time; in the other two patients visualization of the dye preceded the circulation time by 4.7 and 11.5 seconds.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Light, G. A., Livingstone, H. M., and Adams, W. E.: Anesthesia for Operations on the Heart and Great Vessels. Arch. Surg. **60:** 42 (Jan.), 1950.

Preoperative preparation, anesthetic management, and postoperative care for 60 intrathoracic operations on the heart and great vessels are discussed. The group was about equally divided between good and poor risks; there were 6 deaths during the operative and post-operative period, none of which were attributed to anesthetic management. Ether, chosen as the chief anesthetic component for the majority of cases, was administered with positive pressure during inspiration and expiration while the chest was open. Positive pressure accompanying spontaneous respiration was credited with the maintenance of adequate ventilation without overactivity of respiratory movements.

A résumé of the anesthetic management of 16 diagnostic catheterizations of the heart is also presented. Since this procedure involves little sensory stimulation, it was performed with local skin anesthesia. In children under 14, additional basal narcosis with either rectal tribromethanol or Thiopental was employed.

KING

THROMBOEMBOLIC PHENOMENA

Johnson, C. C., and Baggenstoss, A. H.: Mesenteric Vascular Occlusion. I. Study of 99 Cases of Occlusion of Veins. Proc. Staff Meet., Mayo Clin. **24:** 628 (Dec. 7), 1949.

The authors report on a series of 99 cases of mesenteric venous occlusion which were not a result of hernia strangulation, volvulus or intussusception. Occlusion was of the superior mesenteric system in 93 cases and of the inferior mesenteric system in 6. Interference with venous return of blood, whatever the cause of the interference, seemed to be the factor which most often gave rise to the occlusion. Intra-abdominal infection, neoplasm and abdominal surgical procedures seemed to be the leading three causes of interference, in the order given. Infarction was limited to the portion of bowel from which there was interference with the return of venous blood through the vasa recti and arcades. It seems that when thrombosis in a vein of large caliber occurs slowly, the collateral circulation which develops is sufficiently extensive to prevent infarction, providing these small veins (vasa recti and arcades) are not themselves thrombosed.

SIMON

Loewe, L., Lasser, R. P., and Morrison, M.: The Prediction of Thromboembolism. Angiology **1:** 64 (Feb.), 1950.

If prophylactic anticoagulant therapy is to be

selectively employed, there must be some method by which the prethrombotic state may be recognized. Clinical statistics have shown that patients with a past history of thromboembolism or with cardiac disease, especially with hepatic congestion, and patients in the older age group are prone to a high incidence of thromboembolism when exposed to precipitating factors such as bed rest, operative procedures, or major trauma. Additional predisposing factors are obesity, anemia, debility, low total protein, polycythemia, and carcinoma. On the other hand, a substantial number of thromboembolic episodes occur among patients with no known predisposition, and careful dissection of the deep venous system of the legs in unselected autopsy material has revealed the presence of venous thrombi in from 27 to 59 per cent of the cases.

A number of laboratory tests have been employed in an attempt to determine a predisposition to clotting. These tests include platelet count and platelet adhesiveness, antithrombin titer, heparin tolerance, prothrombin time, whole blood coagulation, clot retraction, and fibrinogen B determination. Although some of these tests are promising, no test of sufficient specificity, reliability, and reproducibility has been found. Moreover the importance of local factors and of the vein wall itself has not as yet been defined.

WESSLER

VASCULAR DISEASE

Becker, G. H., Meyer, J., and Necheles, H.: Fat Absorption and Atherosclerosis. Science **110:** 529 (Nov. 18), 1949.

Chylomicrons are macromolecular bodies containing largely neutral fat and some cholesterol. Using a dark field technic for the estimation of chylomicronemia, the authors studied fat absorption in 30 young and 30 old subjects, with average ages of 18 and 76 years, respectively. In persons over 50 years of age, ingestion of a small amount of oleomargarine was followed by an almost twenty-four-hour increase in the chylomicron count in the serum. In younger persons the curve returned to fasting levels within five hours. If it is true that particulate fat circulating in the blood leads to atherosclerosis, it is significant that increased numbers of fat particles circulate in the blood of older persons almost continuously. Administration of lipase or of a detergent (Tween 80) with the fat meal reduced the chylomicron counts and the duration of increased counts of old subjects to levels of young subjects.

WAIFE

Bosher, L. H., Jr., Harper, F., and Bigger, I. A.: A Study of the Collateral Circulation after Excision of Arteriovenous Fistulas. Surgery **26:** 918 (Dec.), 1949.

The authors studied the changes in the collateral circulation following excision of experimentally produced arteriovenous fistulas in dogs. The ramifications and extent of the collateral circulation were visualized with the use of Diodrast. It was found that as early as four days after fistulectomy a marked contraction of the collateral bed occurred. The rapidity with which this took place suggested that the responsible agent was mechanical factors associated with altered blood pressure and blood flow rather than the biologic factor of disuse or lack of need.

ABRAMSON

Schloss, G., and Shumacker, H. B., Jr.: Studies in Vascular Repair. IV. The Use of Free Vascular Transplants for Bridging Arterial Defects. An Historical Review with Particular Reference to Histological Observations. Yale J. Biol. & Med. **22:** 273 (Jan.), 1950.

The authors present a historical review of the subject of vascular transplants, from which review certain concepts arise. There is general agreement that fresh arterial autografts survive as living structures with either no change or only intimal thickening, while fresh venous autografts, although also surviving, undergo more marked histologic changes consisting chiefly of fibrous reinforcement. These alterations are probably due to the effect of the arterial pressure on the graft. Fresh arterial and venous homografts generally show signs of destruction and of reinforcement by connective tissue proliferation from the host. The same type of reaction is noted in fresh arterial heterografts. In spite of marked differences in the histologic alterations, all types of vascular transplants are capable of functionally bridging arterial defects.

ABRAMSON

Gofman, J. W., Lindgren, F., Elliott, H., Mantz, W., Hewitt, J., Strisower, B., Herring, V. and Lyon, T. P.: The Role of Lipids and Lipoproteins in Atherosclerosis. Science **111:** 166 (Feb.), 1950.

By a special ultracentrifugation technic, the authors found a new series of cholesterol-bearing giant molecules in the sera of rabbits fed a high cholesterol diet. The presence of these molecules was associated with mild to severe atherosclerosis. The period (thirty–forty days) of the development of the macromolecules coincided with the development of the vascular lesions. These giant low density molecules have less protein per molecule than the majority of cholesterol-bearing lipoproteins.

Analyses of over 600 human sera are presented. The incidence of measurable concentrations of the giant molecules was significantly higher in normal men than in women in the 20 to 40 year age group. Assuming these molecules reflect the metabolic disturbance resulting in atherosclerosis, the data is in accord with the fact that women of this age group

are less likely to show significant atherosclerosis than men. With an increase in age, significantly larger concentrations of these molecules are found, and the sex difference decreases. Diabetics as a group seemed to show a higher incidence of the molecules than nondiabetics. One hundred and one of 104 patients with proved myocardial infarction (almost all due to coronary artery atherosclerosis) showed high concentrations of this component. A preliminary study of 20 patients on a cholesterol and fat restricted diet revealed a definite reduction in concentration of the abnormal lipid molecules in 17 cases studied within 2 weeks to 1 month. Total serum cholesterol concentrations were not related to the qualitatively different molecules.

WAIFE

Bauer, G.: Patho-Physiology and Treatment of the Lower Leg Stasis Syndrome. Angiology **1:** 1 (Feb.), 1950.

According to the author, incompetence of the deep veins of the leg does not permit the effective propulsion of venous blood by muscular contraction and thereby favors permanent venous stasis. This stasis is responsible for the lower leg syndrome which manifests itself by chronic edema, induration, ulceration, and pain. Popliteal vein ligation, it is claimed, re-channels blood through numerous fine-calibered vessels into the muscle veins of the thigh, eliminates back flow, and relieves the lower leg syndrome.

One hundred ninety-four popliteal vein ligations were performed by the author in patients with the lower leg syndrome. Immediate results showed marked improvement in all patients. There were no postoperative deaths and no complications of any kind except for hematoma in 4 cases. The author cautions that the follow-up period has been too short for final evaluation of the procedure. However, among 78 patients who have been followed for one year, 64 have shown steady progress toward complete healing, 9 have shown relapse, and 5 have had serious recurrence. These latter 14 cases are discussed in some detail.

WESSLER

Pratt, G. H.: The Present Status of Sympathectomy in the Treatment of Vascular Diseases. Angiology **1:** 9 (Feb.), 1950.

In vascular lesions one is concerned particularly with overactivity of the sympathetic system on both the arterial and venous side. The development of sympatholytic drugs has not replaced surgical sympathectomy. The author has found surgical sympathectomy of value in Raynaud's disease, causalgia, Sudeck's atrophy, hyperhidrosis, injury, embolism and aneurysm involving arteries, the post thrombotic syndrome, and occlusive arterial disease. Sympathectomy has not been found to precipitate gangrene in this last group. Patients with post-thrombotic syndrome and occlusive arterial disease must be properly selected if acceptable results from sympathectomy are to be anticipated. Proper selection requires knowledge of the stage of the patients' disease, the accomplishment of an adequate operative procedure, and the realization that sympathectomy will not cure the basic disease process. Operative technics for sympathectomy are discussed.

WESSLER

deTakats, G., and Evoy, M. H.: Lymphedema. Angiology **1:** 73 (Feb.), 1950.

The authors present their observations on 150 cases of lymphedema. The cases were classified as follows: congenital 28, traumatic 11, inflammatory 58, degenerative (malignant) 22, and idiopathic 31.

Acute lymphedema, if treated early and intensively, responds well and leaves relatively little irreversible edema and fibrosis. The measures employed in all cases included elevation of the involved extremity, frequent active movement (except in acute spreading lymphangitis), and elastic compression. Mercurial diuretics were restricted to patients in whom other methods of rapid release of edema were not indicated or were impossible. Heparin was employed in all lymphatic obstructions which accompanied iliofemoral thrombophlebitis. Dicumarol was considered an unsatisfactory anticoagulant. Sympathetic block was used in the vasospastic group. X-ray was utilized in patients with lymphatic streaks, hyperplasia of lymph glands, and lymphorrhea following operations on lymphedematous extremities.

In the treatment of chronic lymphedema, elevation, support, low-salt diet, water restriction and occasionally x-ray therapy were used. Surgery was undertaken only when extremities were painfully heavy, wearing of shoes was difficult, or when ulceration or draining cutaneous lymph cysts appeared. A modified Kondoleon operation was employed in 28 cases; results were satisfactory in 17, doubtful in 5, and poor in 6. The congenital group appeared to do better than the inflammatory group. Cosmetic results were not, however, striking.

WESSLER

Campbell, D. A., and Smith, R. G.: The Arteriographic Examination of the Lower Extremities. Angiology **1:** 100 (Feb.), 1950.

The authors report their experience with Diodrast arteriography of the lower extremities based on more than 300 injections. Complications noted were perivascular infiltration of Diodrast, arterial spasm, hematoma, and pain at the injection site. None of these complications, if properly treated, were considered deterrents to the procedure. Contraindications were limited to a non-pulsatile vessel at the injection site, Diodrast sensitivity, and body de-

formity severe enough to interfere with adequate roentgenographic visualization. The authors do not believe that disease of the vessels to be injected constitutes a contraindication.

The value of the procedure is based on the fact that it provides direct visualization of arterial obstruction and collateral circulation. This, according to the authors, is of assistance in the teaching of vascular diseases, in etiologic diagnosis, estimation of prognosis, determination of amputation level, surgical removal of segmental major vessel occlusion, and possibly selection of candidates for sympathectomy. The authors emphasize, however, that arteriography is only a supplementary test, that its use should be restricted to well-organized clinics, and that it is of limited value to the clinician experienced in peripheral vascular disease.

WESSLER

Poppen, J. L.: Cerebral Arteriography. Surg., Gynec & Obst. **90:** 248 (Feb.), 1950.

The author attributes lack of serious sequela in over 1000 injections of radiopaque dye into the cerebral vessels largely to the fact that injections were made while the patient was under Pentothal anesthesia. He prefers to use 35 per cent Diodrast, injected into one of the carotid arteries in the neck. He advocates visualization of cerebral arteries when aneurysms are suspected. Since more than one aneurysm may be present, demonstration of size and site may be extremely helpful in determining if carotid artery ligation or the intracranial approach is the method of choice. Cerebral arteriography aids also in differentiating brain tumor from cerebral vascular disease. Visualization of the cerebral blood supply should be helpful to the neurologic surgeon in preserving adequate circulation after removal of some of the contents of the skull, thus aiding not only in the diagnosis and localization but also in the prognosis.

SCHWEDEL

OTHER SUBJECTS

Hoobler, S. W., Malton, S. D., Ballantine, H. T., Jr., Cohen, S., Neligh, R. B., Peet, M. M. and Lyons, R. H.: Studies on Vasomotor Tone. I. The Effect of The Tetraethylammonium Ion on the Peripheral Blood Flow of Normal Subjects. J. Clin. Investigation **28:** 638 (July), 1949.

Tetraethylammonium chloride (TEAC) blocks sympathetic and parasympathetic impulses at the autonomic ganglia. When 500 mg. were given intravenously it significantly increased the blood flow to the feet in normal subjects and produced vasodilatation in the hand in seven of eight instances. Circulation in the forearm and calf was increased only slightly. Digital skin temperatures were increased.

The compound did not produce vasodilatation after an extremity had been sympathectomized. Therefore, its vasodilator action is the result of the inhibition of sympathetic vasoconstrictor tone, and not the result of any direct action on the blood vessels.

Since lumbar paravertebral block was about twice as effective as TEAC in increasing blood flow to the foot, the dosage usually used may not cause complete sympathetic blockade.

The increase in blood flow to the foot of normal subjects as a result of TEAC administration is much greater than after aminophyllin, Papaverine, nicotinic acid, and nitroglycerin and slightly greater than the vasodilatation resulting from prolonged body heating.

WAIFE

Humphrey, J. H., and Pagel, W.: The Tissue Response to Heat-Killed Streptococci in the Skin of Normal Subjects, and in Persons with Rheumatic Fever, Rheumatoid Arthritis, Subacute Bacterial Endocarditis and Erythema Nodosum. Brit. J. Exper. Path. **30:** 282 (Aug.), 1949.

The authors report a study of the tissue response to heat-killed streptococci by determining the skin reaction of normal subjects, and of persons with rheumatic fever, rheumatoid arthritis, subacute bacterial endocarditis and erythema nodosum. The strains of streptococci used were all derived originally from human sources and were selected so as to represent Lancefield groups A, B, D. and three different Griffith types. A strain of *Streptococcus viridans* was also included. In a few instances patients were tested with strains of non-hemolytic and α-hemolytic streptococci derived from blood cultures of cases of subacute bacterial endocarditis. In one instance a patient with rheumatic fever was tested with a strain of β-hemolytic streptococcus derived from his own throat cultures.

In normal subjects the Group A strains gave rise to moderate reactions. In the rheumatic fever group they were greatly increased. The patients with rheumatoid arthritis reacted rather less intensely than the normal group and those with subacute bacterial endocarditis gave very small reactions even with their endogenous strains. Apart from the fact that the Group A strains gave the most intense reactions there was no obvious correlation between the severity of the reactions and any of the known antigenic components of the streptococci.

BELLET

Dock, W., and Taubman, F.: Some Technics for Recording the Ballistocardiogram Directly from the Body. Am. J. Med. **7:** 751 (Dec.), 1949.

The authors present three simplified technics for ballistocardiography which obviate the disadvantages of the bulky, expensive, and fixed ballistocardiographic installation. With a portable electrocardiograph, satisfactory records may be obtained

directly from the body by use of a sphygmograph applied to the head, a photocell partly shaded by a ruler across the shins, or by a coil in a magnetic field.

HANNO

Lewis, Jr., J. L., and Terry, L. L.: Electrokymography—An Appraisal of its Present Clinical Status. Ann. Int. Med. **32:** 36 (Jan.), 1950.

It would appear that the primary application of the electrokymograph at the present time, is as a physiological research tool. In its present state of development it is for the clinical investigator rather than for the clinician.

Electrokymographic tracings show a considerable range of variation in normal subjects. As a consequence of the paucity of data with regard to what is normal and what is not, interpretation is uncertain. Lack of wave amplitude standardization is another hindrance to interpretation. The disadvantages of the device are the expensive equipment and trained personnel required for operation; the small area recorded at one time, making multiple views necessary; and the lack of standardization. An attempt was made to discover if etiologic types or patterns of heart disease could be found by this means. The results have been disappointing to date. Mechanical alternans is well demonstrated, and has been discovered occasionally where clinically unsuspected. Insofar as mechanism disturbances are concerned, it would appear shat the electrokymogram is seldom diagnostic, as the electrocardiogram nearly always is. Although it is in the study of myocardial infarction that the electrokymograph might seem to give the most concrete immediate results, here also results are often equivocal. Valvular defects may be present, and yet apparently produce no recognizable change from the normal in the electrokymogram.

WENDKOS

Milnor, P., Burch, G., Ray, T., Threefoot, S., and Berenson, G.: Considerations of Renal, Hepatic, and Extremital Arteriovenous Differences in Concentration of Radiomercury of a Mercurial Diuretic. J. Clin. Investigation **29:** 72 (Jan.), 1950.

The authors studied the problem of mercurial clearance by tracing Mercuhydrin labeled with radioactive mercury. In 7 subjects who had not had a mercurial diuretic within five days, either right renal catheterization or hepatic venous catheterization was performed. A measured quantity of Mercuhydrin labeled with Hg 203 and 205 was injected into a vein of an extremity over an interval of fifteen to forty seconds. Simultaneous samples of blood were then collected at frequent intervals from the right renal vein or hepatic vein, the femoral artery and an unused peripheral vein. Almost simultaneous urine samples were collected either from uretral or vesical catheters. Reabsorption of mercury from the bladder was ruled out.

The percentage extraction of mercury by the kidney, extremity and liver were then calculated. While the studies were subject to certain limitations, it was found that renal extraction of radioactive mercury varied from 5 to 25 per cent between ten and ninety minutes after injection. In a control subject the hepatic extraction was 5 to 10 per cent during this time interval, but in a subject in congestive heart failure no hepatic extraction was detected. A temporary decrease in urinary rate of volume flow was found to precede the usual mercurial diuresis and this decreased rate of flow coincided with the appearance of mercury in extremely high concentrations in the urine.

BUTTERWORTH

Ellis, E. J., Essex, H. E, and Edwards, J. E.: Lesions of the Heart in Dogs following Cardiac Catheterization. Proc. Staff Meet., Mayo Clin. **25:** 73 (Feb.), 1950.

The right side of the heart of 16 dogs was catheterized in a manner simulating the procedure performed on human beings. Nine of the 16 dogs exhibited thrombotic lesions. Two of these showed mural thrombosis in the right atrium and superior vena cava. In 3 dogs lesions coexisted in the right ventricle and atrium. In the remaining 4 dogs the lesions were mural thrombi restricted to the right atrium. The right atrial thrombi were associated with necrosis of the underlying myocardium. No emboli were found in the lungs.

The authors believe it is doubtful that lesions occur as commonly in human patients after catheterization. No deaths attributable to lesions similar to those encountered in the present study have been reported. The incidence of the lesions themselves seems low but several cases are reported in which mural thrombi were discovered at autopsy following a catheterization procedure.

SIMON

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A. H. A. FELLOWSHIPS

Applications for Established Investigators and for Research Fellows must be received by September 15, 1950. Information and forms may be obtained from the Medical Director.

$4,000,000 RAISED IN HEART CAMPAIGN

Before retiring as President of the American Heart Association, Dr. H. M. Marvin announced that approximately $4,000,000 had been collected from the public in the 1950 heart campaign to support research, education, and community service in the cardiovascular field. This amount compares with $2,600,000 raised in 1949.

Dr. Marvin pointed out, "This increased financial support by the public will make possible expanded research programs and intensified activity in bringing the benefits of present knowledge and new discoveries to the public throughout the country. For the year 1949, the American Heart Association and its affiliates allocated close to $750,000 for worthy research projects. Incomplete figures for the year 1950 indicate that the total allocated for research by the national office and the affiliates will be over $1,000,000 or more than 25% of the $4,000,000 raised nationally during the 1950 campaign."

AMERICAN COUNCIL ON RHEUMATIC FEVER

Dr. T. Duckett Jones, Medical Director of the Helen Hay Whitney Foundation, New York, has been elected Chairman of the American Council on Rheumatic Fever of the Association. Dr. Arthur C. DeGraff, Professor of Therapeutics, New York University College of Medicine, was named Vice-Chairman. Dr. Francis F. Schwentker, Baltimore, Md.; Dr. Rustin McIntosh, New York, N. Y.; Dr. George M. Wheatley, New York, N. Y., and Dr. Hugh McCulloch, Chicago, were elected to the Executive Committee.

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will conduct its 32nd Annual Session at St. Louis, April 9–13, 1951. Dr. Ralph Kinsella, St. Louis, is the General Chairman, responsible for the program of Clinics and Panel Discussions. Dr. William S. Middleton, President of the College, will be in charge of the program of Morning Lectures and afternoon General Sessions.

The College has also announced that a limited number of Research Fellowships in Medicine will be available from July 1, 1951 to June 30, 1952. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians in the early stages of preparation for a teaching and investigative career in Internal Medicine. Application forms may be obtained before October 1 from the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

INTERNATIONAL SOCIETY OF ANGIOLOGY

The first meeting of the recently founded International Society of Angiology will be held in Paris, September 4–5, 1950, at the College de France, Place Berthelot. The officers of this society are: Dr. Rene Leriche, Paris, President; Drs. Emile Holman, San Francisco, Alexander M. Boyd, Manchester, and Fernando Martorell, Barcelona, Vice-Presidents; Dr. Henry Haimovici, New York, Secretary. All correspondence regarding the Society and its first meeting should be addressed to Dr. Haimovici, 1148 Fifth Avenue, New York 28, N. Y.